BULLETIN
OF
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(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

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SALICYLATE AND RHEUMATIC ACTIVITY

An Objective Clinical-Histologic Study of the Effect of Salicylate on Rheumatic Lesions, Those of Joints and Tendon Sheaths in Particular

GEORGE E. MURPHY[1]

From the Department of Pathology, The Johns Hopkins Hospital and Medical School

In view of the many statements concerning the remarkable effect of salicylate in bringing about a rapid improvement in the actual pathological state of the affected joints of active rheumatic subjects, it is rather remarkable that, as far as the writer has been able to determine, there has never been reported a truly objective study of the effect of salicylate upon the inflammatory exudate of rheumatic joints.

HISTORICAL

In 1881, 7 years after introducing salicin, the bitter glycoside of willow bark, into medicine for the treatment of rheumatic fever, Thomas Maclagan (1) of Edinburgh was of the opinion that salicylate exerted a "distinctly curative effect on the rheumatic inflammation of the joints." His considerable clinical experience in this field led him furthermore to conclude that salicylate "if given in sufficient quantity to destroy the rheumatic poison before this has begun to affect the heart, cannot fail to prevent cardiac complications." Once affection of the heart had occurred, salicylate, he felt, "curtails the duration and limits the extent of the rheumatic poison on the heart." Stricker, (2) having introduced salicylic acid in the treatment of rheumatic fever into Germany in 1876, felt that this acid could be expected "to prevent the occurrence of fresh attacks in hitherto unaffected joints, and secondary inflammation of other serous membranes, especially endocardium." Lees (3) in his Harveian lecture of 1903 concluded from clinical observations made principally at the Great Ormond Street hospital that salicylate "is as truly anti-rheumatic as quinine is anti-malarial or mercury anti-syphilitic," provided adequate dosage, 150 to 200 grains daily, is maintained. And Clarke (4), 3 years later, in recording his results in acute rheumatic patients over 12 years of age treated with 240 grains or more of sodium salicylate daily, stated that salicylate "reduces the fever, relieves the pain and swelling, and shortens the course of the disease," and "appears by quickly cutting off the disease to offer protection to the heart."

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A widespread clinical belief that the inflammation of rheumatic joints regresses promptly under salicylate persists to the present time. In 1938, Sheldon (5), at the International Congress of Rheumatism, stated that "Provided the dose is adequate there is no doubt that the disease is considerably curtailed as judged by the subsidence of the articular inflammation." Goodman and Gilman (6), in 1941 expressed the opinion that "salicylates reduce the pain, immobility, swelling and inflammation of the joints in acute rheumatic fever," and that "usually within 24 to 36 hours there is apparent improvement or complete relief of pain, swelling, immobility, local heat and redness of the joints," and that "Complete relief is obtained in over 80 per cent of acute cases and failure occurs in only 1 to 2 per cent of patients. Barr (1940) (7) states that in the case of rheumatic fever, "In response to therapeutic doses (of salicylate, cinchoninic acid derivatives and aminopyrine, G. M.) the fever falls precipitously to normal, other evidences of toxemia disappear, and arthritis rapidly subsides." Lichtwitz (8) in 1944 expressed the opinion that salicylates "exert a remedial effect not merely upon fever and pain, but also upon the initial edema which in rheumatic fever precedes the irreversible tissue degeneration that, in turn, evokes defense of inflammation. This action of antipyretic substances can be conclusively demonstrated in joints, and presumably occurs in other tissues as well." Taran and Jacobs (9) in the conclusion to a recent (1945) study of rheumatic children state that: "Large doses of salicylates produce a prompt and effective subsidence of all clinical and laboratory evidence of rheumatic activity in children having rheumatic polyarthritis. Massive doses of salicylates in acute rheumatic carditis are equally effective in promptly suppressing all clinical and laboratory evidence of rheumatic activity."

While these beliefs in the effect of salicylates upon rheumatic inflammation may be true, they have not been *proven* to be true by any objective study. The usually dramatic effect of salicylates in lowering body temperature and in relieving joint pain and tenderness, may strongly influence one's opinion of the actual state of the joint lesion. In view of the widely accepted claims that are made for salicylates as drugs which not only bring about a prompt reabsorption of rheumatic inflammatory exudate but also prevent rheumatic damage, it seemed of some importance to the writer to attempt to acquire objective information regarding the effect of salicylate on rheumatic joint and tendon sheath lesions. For if it be proven that salicylates prevent or cause a rapid regression of the rheumatic process in these sites, it might be expected that they may prevent or cause regression of the rheumatic process in more important sites, namely the heart and lungs. Coburn (10) recently, after a controlled clinical study, in which considerable emphasis was placed on the course of the blood sedimentation

rate in rheumatic patients treated with large doses of salicylates, concluded that his observations indicated that "the inflammatory reaction of rheumatic fever can be suppressed to a degree that the disease process is not detectable by clinical or laboratory examinations, and suggest that the prompt suppression of rheumatic inflammation may prevent the development of the stigmata of heart disease. This effect appears to parallel and be dependent upon the concentration of salicylate in the circulating plasma."

It has long been known that salicylate rapidly and effectively decreases the body temperature of febrile patients, there occurring a concommitant decrease in pulse rate (this effect rarely obtaining when body temperatures are normal). The mechanism of this antipyretic effect is not clear. Heat production is apparently not inhibited but heat dissipation is thought to be augmented by increased peripheral blood flow and sweating. Elevated body temperature may be lowered, however, even if sweating is prevented by atropine. The well-recognized analgesic effect of salicylate is even more poorly understood.

In 1923, Boots and Swift (11), from a careful study of the character of the synovial exudate aspirated from affected joints of patients with serum sickness, concluded that "the synovial exudate (from the arthritis of serum sickness) is microscopically indistinguishable from that occurring in joints of patients with rheumatic fever." Recently, Rich and Gregory (12) (13) (14) have shown that rabbits subjected to experimental serum sickness develop, in some cases, cardiac, pulmonary, and joint lesions that, in their basic characteristics, resemble closely those respectively of rheumatic carditis, pneumonitis, and arthritis. In 1922, Swift (15) reported that rabbits treated with sodium salicylate in daily doses of from .16 to .2 gm. per kilo. of body weight, and at the same time immunized with intravenous injections of streptococcus viridans, both living and in vaccine form, and also with washed sheep erythrocytes, showed diminished complement-fixing antibodies, agglutinins and hemolysins when compared with controls similarly immunized. If the antigens were treated with sodium salicylate in vitro and subsequently injected intravenously into rabbits, the animals usually showed a lower antibody titer than did rabbits receiving the untreated antigen intravenously and sodium salicylate by stomach tube. In 1927, Derrick, Hitchcock, and Swift

(16) reported studies in which they were unable in most cases to detect a rise in titre of anti-horse serum precipitins in patients who received large amounts of anti-pneumococcus horse serum followed immediately by 6 to 10 gm. of acetylsalicylic acid or neocinchophen for 10 to 14 days. These patients "escaped arthritis" of serum sickness. The criteria for determining arthritis appeared to have been based on pain and tenderness; the absence of these symptoms in the treated patients may have been due to the analgesic effect of the drugs. It is particularly noteworthy, however, that the drugs did not prevent the development of urticaria, which appeared by and large to these investigators to have been more intense in the treated than in the untreated patients. While this study has been regarded as providing evidence that salicylates prevent tissue damage by suppressing antibody formation, the development of urticaria makes it evident that the drugs did not really suppress antibody formation or prevent the antigen-antibody reaction which cause local tissue damage.

Following up this latter work Schlesinger, in the hope of preventing rheumatic recrudescences, began the use of salicylate immediately following the onset of pharyngitis or tonsillitis in rheumatic subjects—20 to 30 gr. daily for 4 weeks. 8 years later (1938) he reported in his Milroy lectures (17) that "with this form of prophylactic therapy, serious relapses following tonsillitis rarely arise. When fresh rheumatism or carditis does occur, it takes a much milder form, and virulent fatal forms of pericarditis are now seldom encountered. In some way the aspirin damps down the whole rheumatic process, and the intervening 'silent' period between throat infection and relapse is often prolonged. Acute rheumatic fever with high temperature and considerable illness is replaced by a relatively milder form of 'miniature rheumatic fever'—on the same grounds a course of aspirin should be given rheumatic children as a routine after tonsillectomy."

Graef and his associates (18), in 1933, after following 105 acute rheumatic patients receiving no form of therapy which might be believed to be specific and no antipyretic drug, called attention to the tendency of acute manifestations of rheumatic fever to subside spontaneously and often rapidly. Coburn and Kapp (19) in 1943, reported in vitro studies showing that sodium salicylate modified the precipitation of normal rabbit serum euglobulin by its antiserum. They

further observed that sodium salicylate added to a system containing crystalline egg albumin and its antibody partly prevented the formation of precipitate, the degree of inhibition being related to the concentration of salicylate, and that the salicylate effect on immune precipitation was reversible and appeared to be due to inactivation of antibody. Salicylate appeared to be more effective in preventing specific precipitation than other lyotropically powerful ions such as thiocyanate and iodide. In the same year Coburn and Moore (20) reported their study of 186 young rheumatic subjects before and following β. hemolytic streptococcal pharyngitis. Throat cultures in 47 of this group contained β. hemolytic streptococci, group A, and these 47 patients received 4 to 6 gm. of sodium salicylate daily for 4 weeks. Of this group "46 escaped and 1 developed rheumatic fever." 15 of these 47 treated with salicylate showed a "brief asymptomatic rise in sedimentation rate within a few days after prophylaxis was discontinued." None of these developed symptoms or signs of rheumatic activity. 31 maintained normal sedimentation rates and escaped both clinical signs and symptoms of rheumatic disease. Of the 139 untreated control group 82 escaped and 57 were reported as developing a rheumatic recrudescence. The criteria for determination of rheumatic activity in this group of patients were not stated. The circulating anti-β streptolysin response in both salicylate treated and untreated groups was reported as being similar.

Finally, Brodie, Udenfriend, and Coburn (21) have described a method for the determination of the salicyl radicle in oxalated blood, and Coburn has suggested a therapeutic technique for the rapid development and maintenance of plasma salicylate levels above 350γ per cc., inasmuch as his observations suggested that a "plasma salicylate level of at least 350γ per cc. may be required to suppress the rheumatic reaction and that plasma levels below 200γ per cc. may be sufficient to relieve symptoms while masking a progressive inflammatory process."

Fortunately, during the period of the present study, the medical service of the Johns Hopkins Hospital has been treating active rheumatic fever with large doses of salicylates with frequent determinations first of plasma salicyl and subsequently serum salicyl levels. Through the kindness of Dr. Warfield T. Longcope and Dr. Edwards A. Park

the writer has had the opportunity to study 10 actively rheumatic patients on the medical service and 1 actively rheumatic patient on the pediatric service, all of whom received large doses of salicylates.

MATERIALS AND METHODS

Preliminary observations began in the spring of 1944 with day to day recordings of measured size (in cm.) of rheumatic joints. In the case of each joint to be followed the site of maximal swelling was determined as closely as possible. A thin metal tape was applied around the circumference of the joint, passing directly over the site of maximal swelling and this measurement recorded. With the tape still applied, skin pencil or gentian violet lines were drawn at both margins of the tape around the circumference of the joint, and at each subsequent measurement the tape was placed between these lines. Before, during, and since completion of the study, the writer has measured with the metal tape similarly marked joints of normal subjects from day to day, each day recording the measured figure on a fresh sheet of paper, and was able to obtain figures consistent often within one quarter of a centimeter and always within one half centimeter. During the study, each set of daily joint measurements were recorded on a fresh sheet of paper, without reference to preceding measurements. Evaluation of change in tenderness, though lacking in objectivity, was attempted, and the relative tenderness from day to day recorded. Evaluation of change in local heat by manual estimation, and of redness by visual estimation, were attempted, but found to be too gross to be of any significance. In the last 6 of the last 7 cases studied a thermocouple (Taylor Instrument Co. "Dermatherm") was used. This instrument is in wide use for the measurement of skin temperature. A small circle was drawn with heavy skin pencil or gentian violet over the part which appeared to be most involved. The "hot" junction was applied to the skin within the circle until a maximum reading on the millivoltmeter was obtained, this procedure being repeated until a constant reading at each time of measurement was obtained. The 6 actively rheumatic patients, in whom temperatures of the skin overlying involved joints were taken, were at complete bed-rest throughout the study with the exception of 1 who was

out of bed only during the time she was transferred at the end of 6 days from the Baltimore City to the Johns Hopkins Hospital, and 8 days later to the Provident Hospital. Skin temperatures were never taken within 2 hours of a meal. Bed covers were removed and remained off the patient for 10 to 15 minutes before measurements were taken. Room temperature was recorded at the time of each skin temperature measurement. Relative humidity was not recorded, for within the range of room temperatures that prevailed in this study changes in relative humidity must be very considerable before affecting skin temperature. Talbot (22) found in a series of measurements made on 10 subjects at room temperatures of from 20.0°C. to 22.5°C. no consistent change in the skin temperature over different parts of the body when the humidity varied from 30 to 90 per cent. Phelps and Vold (23) found that it would require an increase of 50 per cent in the relative humidity to raise the skin temperature as much as .5 degree C. at room temperatures between 20°C. and 27°C. As Sheard and Williams (24) point out, the vapor pressure at the surface of the skin at 33°C. (91°F.) is 1.47 inches of mercury, whereas in air at 21°C. (70°F.) with a saturation of 80 per cent, it is only .58 in., or a gradient which readily permits full evaporative loss.

Case history 1: V. W., (hosp. no. 318624) a 16 year old white girl was admitted to the Johns Hopkins Hospital on April 6, 1944, complaining of a tender right knee, both elbows and left index meta-carpo-phalangeal joint and stiffness of both wrists. There was no past history of rheumatic fever. The patient stated that in late January, 1944 she developed a sore throat, followed in about 3–4 days by migratory aches and pains with increased heat in the right knee, right elbow, shoulders, feet, and ankles. By late February the elbows, wrists and knees became somewhat stiff with limitation of movement. In the 8 weeks before admission the patient received salicylate to the point of nausea and tinnitus, during which time the patient felt there was some diminution in the tenderness and swelling of her joints.

On examination the faucial tonsils were found to be absent (history of T. & A. several years before). The pharynx grossly appeared normal. An examination was made for tendon sheath and other subcutaneous nodules. None was found. A blowing apical systolic murmur was heard on admission and persisted to discharge 4 months later. The course of the patient before and during salicylate therapy may be followed in Table I.

TABLE I

V. W., 16 Year Old White Female: Clin. Diag., Rheumatic Fever, Active

Body Weight—105 Lbs.

TIME		RIGHT KNEE	LEFT KNEE	LEFT 2ND METACARPO PHALANG	LEFT 5TH PROX. INTER PHALANG	RIGHT WRIST	LEFT WRIST	COR. SED. RATE	DOSES OF NA SALICYL. IM G.	SALICYL. LEVEL	CULTURES
4/6/44 10 P.M.	Size tend.	33.0 ++	33.0	No Swelling or Tenderness	No Swelling or Tenderness	Not Measured					
4/7/44 11 A.M.	Size tend.	33.0 ++	33.0								
4/8/44 10:30 A.M.	Size tend.	33.0 fluc. ++	33.0	++				44			
4/10/44 10:30 A.M.	Size tend.	33.0 fluc. ++	33.5 fluc. + Tapped	12.0 ++	Begin Swelling						Joint fluid 4900 cells/ c.mm.—Over 90% polys. No growth
4/11/44 6 P.M.	Size tend.	33.5 fluc. +	33.5 fluc. +	11.0 +	6.0 +	17.0 +	16.5 +				B. Hem. Strep. fr. thr. & N-P
4/12/44 3:15 P.M.	Size tend.	33.5 Sl. fluc. +	33.5 fluc. 0	10.0 0	6.5 +	17.0 ++	16.5 +				Cath. Urine. No growth

		+	0	0	+	++	+				
4/13/44 2:30 P.M.	Size tend.	34.0 fluc. +	33.5 fluc. 0	10.5 +	6.5 +	17.0 ++	16.25 +				
4/14/44 2:30 P.M.	Size tend.	34.0 +	33.5 Sl. fluc. 0	10.5 +	6.75 +	17.0 ++	16.25 +				B. Hem. Strep. Thr. & N-P.
		salicylate started							6.3		
4/15/44 3:30 P.M.	Size tend.	33.75 +	33.5 0	10.0 +	6.25 +	17.0 +	16.25 +		6.3		Cath. Urine. No growth
4/16/44 5:30 P.M.	Size tend.	33.75 +	33.5 0	10.0 0	6.25 +	17.0 +	16.25 ++	46	6.3	290γ	
4/17/44 5:30 P.M.	Size tend.	33.75 +	33.25 0	10.0 0	6.25 +	17.0 +	16.25 +		6.3		
4/18/44 7:15 P.M.	Size tend.	33.75 +	33.25 0	10.0 0	66.0 +	16.75 +	16.0 +	40	6.3	320γ	
4/19/44	Size tend.	33.75 +	33.25 0	9.75 0	6.0 0	16.75 +	16.0 +		6.3		
4/20/44	Size tend.	33.75 +	33.25 0	9.50 0	5.75 0	16.50 +	16.0 +		6.3		
4/21/44	Size tend.	33.5 +	33.25 0	9.50 0	5.75 0	16.50 +	16.0 0	36	6.3	340γ	

TABLE I—*Concluded*

TIME		RIGHT KNEE	LEFT KNEE	LEFT 2ND METACARPO PHALANG	LEFT 5TH PROX. INTER PHALANG	RIGHT WRIST	LEFT WRIST	COR. SED. RATE	DOSES OF NA SALICYL. IN G.	SALICYL. LEVEL	CULTURES
4/22/44	Size	33.50	33.0	9.50	5.75	16.50	16.0				
	tend.	+	0	0	0	0	0		6.3		
4/24/44									6.3	290γ	
4/26/44	Size	33.5	33.0			16.5	16.0				
	tend.	+	0			0	0		6.3		
4/27/44	Size	33.5	33.5					42			Thr. Heavy growth.
	tend.	+	0						6.3	230γ	B. Strep.
4/30/44										290γ	
5/ 3/44	Penicillin spray to throat and into both nostrils every 2 hours							41		240γ	Norm. Thr. Flora
5/ 8/44	during the day										
5/10/44								40			
5/12/44								39		350γ	
5/15/44										270γ	
5/18/44	33.5 + 33.0							38		280γ	Heavy B. Strep. Thr.
5/22/44								36		370γ	
5/29/44								32		342γ	
6/ 1/44								40		400γ	
6/ 9/44										420γ	
7/21/44								36		324γ	Thr. Normal Flora
8/ 8/44	Patient discharged										
9/ 7/44	Out-patient							6		3 G. Salicyl./day	
9/21/44								8		2 G. Salicyl./day	
10/19/44								4		No Salicyl.	
12/ 7/44	No joint symptoms							5		" "	
1/18/45								7		" "	
3/ 6/45								11		" "	

In a study of Table I the following are evident:

(1) A measurable[2] decrease in the size of the right and left knees could not be detected until the 8th day of salicylate therapy.

(2) The left 2nd metacarpo-phalangeal joint, which was decreasing in size before salicylate was begun, showed on salicylate therapy a continued decrease at about the same rate as before salicylate.

(3) The left 5th proximal interphalangeal joint was decreasing in size before salicylate and did not show a further measurable decrease until the 6th day of salicylate therapy.

(4) A measurable decrease in size of the right wrist occurred on the 7th day of salicylate therapy.

(5) The decrease in size of the left wrist on salicylate proceeded at about the same rate as before salicylate therapy.

(6) During the time joint measurements were made the plasma salicyl levels ranged between 290γ and 340γ per cc.

(7) The corrected sedimentation rate remained above 30 throughout the patient's hospitalization.

Case history 2: E. McN., (hosp. no. 236762) a 29 year old white woman was admitted to the Johns Hopkins Hospital on April 10, 1944 complaining of a painful right knee of about 4 weeks' duration. Twice at the age of 10 years she had attacks of multiple joint pains. About 4½ weeks before admission she developed a sore throat followed in about 4 days by pain, swelling, and tenderness of the joints of her thumbs. The right thumb became asymptomatic in a few days but the tenderness of the joints of her left thumb persisted to admission. 3 or 4 days after the thumbs became involved, both knees became tender, swollen, and painful on motion. The left knee became asymptomatic before admission. On admission the tonsils and pharynx appeared grossly normal. An examination was made for tendon sheath and other subcutaneous nodules. None was found. The course of the patient may be followed in Table II.

A study of Table II reveals the following:

(1) During the 12 days of salicylate therapy on which joint measurements were made (plasma salicyl levels ranging between 320γ and 530γ per cc.) no measurable decrease in size of the clinically involved knees, ankles, or right elbow could be detected.

[2] By "measurable" is meant a difference of .5 cm. in circumference, as this has been found to be the smallest difference that lay outside the limits of error of the method. Smaller differences were not considered significant.

TABLE II

E. McN., 29 Year Old White Female: Clin. Diag., Rheumatic Fever, Active; Rheumatic Heart Disease

30 gr. aspirin for 13 days before admission. Body weight—150 lbs.

TIME		RIGHT KNEE	LEFT KNEE	RIGHT ANKLE	LEFT ANKLE	RIGHT ELBOW	LEFT ELBOW	WINTROBE CORREC. SED. RATE	DOSES OF NA SALICYL. IN G.	SERUM SALICYL. LEVEL	CULTURES
4/10/44	Size	37.5	37.9	No evident swelling, heat,				46			
	tend.	+++	0	or tenderness							
4/11/44	Size	37.5	37.0	27.0	26.0	22.5					Normal throat flora
2 P.M.	tend.	+++	+	++	0	++					
3 P.M.		Na Salicylate begun with 10 g. i.v.							13.0		
8 P.M.	Size	37.5	37.5	27.0	26.0	22.5	23.0				
	tend.	+	++	+	0	++	0				
4/12/44	Size	37.5	37.5	27.0	26.5	23.0	23.0	50	7.0	420γ	
3 P.M.	tend.	+	+	+	++	++	0				
4/13/44	Size	37.5	37.5	27.0	26.0	23.0	23.0		9.0		
2 P.M.	tend.	++	+	+	+	+	0				
4/14/44	Size	37.5	37.5	27.0	26.0	23.0	23.0		5.7	530γ	
2 P.M.	tend.	+	+	+	0	0	+				
4/15/44	Size	37.5	37.5	27.0	26.0	23.0	23.0		5.4		
5 P.M.	tend.	0	0	0	0	0	+				
4/16/44	Size	37.25	37.5	27.0	26.0	23.0	23.0		4.5		
6 P.M.	tend.	0	0	+	0	0	0				
4/17/44	Size	37.5	37.5	27.0	26.0	23.0	23.0		5.4		
5 P.M.	tend.	0	0	0	0	0	0				
4/18/44	Size	37.5	37.5	27.0	26.0	23.0	23.0	42	5.4	330γ	
7. P.M.	tend.	Taut ham str. tendons		0	0	0	0				

4/17/44 5 P.M.	Size tend.	37.5 0	37.5 0	27.0 0	26.0 0	23.0 0	23.0 0		5.4		
4/18/44 7. P.M.	Size tend.	37.5 Taut ham str. tendons	37.5	27.0 0	26.0 0	23.0 0	23.0 0	42	5.4	330γ	
4/19/44	Size tend.	37.5 Taut ham str. tendons	37.5	27.0 0	26.0 0	23.0 0	23.0 0				
4/20/44	Size tend.	37.5 Taut ham str. tendons	37.5	26.75 0	26.0 0	23.0 0	23.0 0		5.4		
4/21/44	Size tend.	37.5 Taut ham	37.5	26.75 +	26.0 +	Not Measured		45	5.4	320γ	
4/22/44	Size tend.	37.5 0	37.5 0	26.75 0	26.0 +				5.4		
4/24/44								37		250γ	
5/ 2/44								31		360γ	
5/ 5/44										370γ	
5/ 8/44										340γ	Thr. Heavy Growth Friedlander's
5/12/44								30		400γ	
5/16/44								30		390γ	
5/19/44								30		310γ	
5/20/44											Normal throat flora
5/24/44								31		322γ	
5/27/44								-			Normal throat flora
5/29/44								31		250γ	
6/ 2/44										219γ	
6/16/44								34		400	
7/ 4/44		Right ankle sl. swollen & tender									
7/ 7/44								49		416γ	
7/11/44								37		416γ	
7/21/44								15		422γ	
7/23/44		Patient is discharged									

TABLE III

L. McK., 18 Year Old White Female: Clin. Diag., Rheumatic Fever, Active

Body Weight—125 Lbs.

TIME		RIGHT KNEE	LEFT KNEE	RIGHT ANKLE	LEFT ANKLE	CORRECTED SED. RATE (WINTROBE)	DOSES OF NA SALICYL. IN G	SALICYL. LEVEL	CULTURES
4/5/44	Size tend.				+	30	10.0		
4/6/44 6 P.M.	Size tend.	36.5 ++	35.5 ++	24.0 0	24.0 0	30	9.3	440γ	
4/6/44 10 P.M.	Size tend.	36.5 +	35.5 +	24.0 0	24.0 0		6.0		
4/7/44 11 A.M.	Size tend.	36.5 +	35.5 +	24.5 0	24.0 0		6.0		
4/8/44 10:30 A.M.	Size tend.	36.0 +	35.5 +	24.0 +	24.0 0	28	7.2	630γ	
4/10/44 10:30 A.M.	Size tend.	36.0 +	35.5 +	24.0 0	24.0	28	7.2	440γ	
4/11/44 6 P.M.	Size tend.	35.5 0	35.5 0	24.0 0	24.0 0		7.2		Normal throat flora
4/12/44 3 P.M.	Size tend.	35.5 0	35.0 0	24.0 0	24.0 0		7.2	380γ	
4/13/44 2:30 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0		7.2		
4/14/44 2:30 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0	30	7.2	360γ	

	tend.	0	0	0	0				
4/14/44 2:30 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0	30	7.2	360γ	
5/15/44 3 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0		7.2		
4/16/44	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0		7.2		
4/17/44 6 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0		7.2		
4/18/44 7:30 P.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0	26	7.2	330γ	
4/19/44	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0		7.2		
4/21/44 8:30 A.M.	Size tend.	35.5 0	34.75 0	24.0 0	24.0 0	19	7.2	340γ	
4/27/44						16		360γ	
4/29/44		Patient complains of sore throat							Sl. growth B. Hem. Strep. from throat
5/ 5/44		Sulfadiazene spray to throat and into both nostrils				11		345γ	Heavy growth B. Strep. from throat
5/ 8/44									
5/12/44						18		420γ	
5/16/44						19		385γ	Heavy growth B. Strep. from throat
5/19/44						15		485γ	
5/24/44		Penicillin Spray				12		265γ	Sl. growth B. Strep. from throat
5/27/44									
6/ 1/44		Salicylate stopped							
6/10/44		Patient discharged				12			Normal throat flora

(2) During 90 days of salicylate therapy the corrected sedimentation rate remained above 30.

Case history 3: L. McK., (hosp. no. 318130) an 18 year old white girl was admitted to the Johns Hopkins Hospital on April 15, 1944 complaining of painful, swollen joints since September, 1943. There was no past history of rheumatic fever. She denied a history of preceding or subsequent upper respiratory infection. In late September, 1944 she developed a painful, swollen right knee, followed in about one week by involvement of the left ankle. In following weeks both elbows, wrists, right ankle, and shoulder joints became involved. She remained at her work as an assembly woman in an aircraft factory, receiving periodic heat therapy. In the 2 to 3 days immediately preceding admission the above-mentioned joints became increasingly tender and painful.

On admission the faucial tonsils grossly appeared normal as did the pharynx. An examination was made for tendon sheath and other subcutaneous nodules. None was found. There was no clinical evidence of heart disease. The course of the patient on salicylate therapy may be followed in Table III.

In Table III it may be seen that:

(1) No measurable decrease in size of the clinically involved right knee could be detected before the 5th day, and of the left knee before the 8th day of salicylate therapy.

(2) The plasma salicyl determinations varied between 330γ and 630γ per cc. during the period of joint measurements.

(3) The corrected sedimentation rate did not fall below 15 until after 30 days of salicylate.

Case history 4: F. K. J., (hosp. no. 319945) a 20 year old colored male was admitted to the Johns Hopkins Hospital on April 30, 1944, complaining of a tender swollen right ankle, and stiffness with pain on motion in the elbow and finger joints. Eleven years before this admission he experienced an attack of swollen, painful knees which the patient stated was not preceded by a sore throat. This attack cleared symptomatically without bed-rest in about 2 weeks. Eight years before this admission, following in 2 to 3 weeks a sore throat, he developed rather severe polyarthritis, affecting particularly the knees which became swollen and tender, associated with dyspnea forcing him to bed for one week. About 8 weeks later he developed a sore throat severe enough to cause discomfort on eating. Within a few days the patient first became aware of a nodule in the left palm and one at the right elbow. On admission one week later subcutaneous nodules were found over the lateral aspects of both patellae, on the dorsum of both feet, over the lateral humeral epicondyles, and over the flexor tendons of the left palm. There was clinical evidence of rheumatic heart disease. On admission the corrected sedimentation rate was 21. For 10 days the patient received 2.4 gms. of sodium sali-

cylate daily. Eighteen days later he was discharged with a corrected sedimentation rate of 42. Eight years and four months later the patient, now 20 years of age, was readmitted to the Johns Hopkins Hospital (the present admission). Two weeks prior the patient experienced mid-abdominal pain which passed in about 15 to 20 minutes after going to bed. Later the same day pains occurred in both shoulders. Dull substernal pain was also felt. The shoulder pain ceased in 2 or 3 days. Meanwhile he became aware of tenderness and swelling in both elbows,

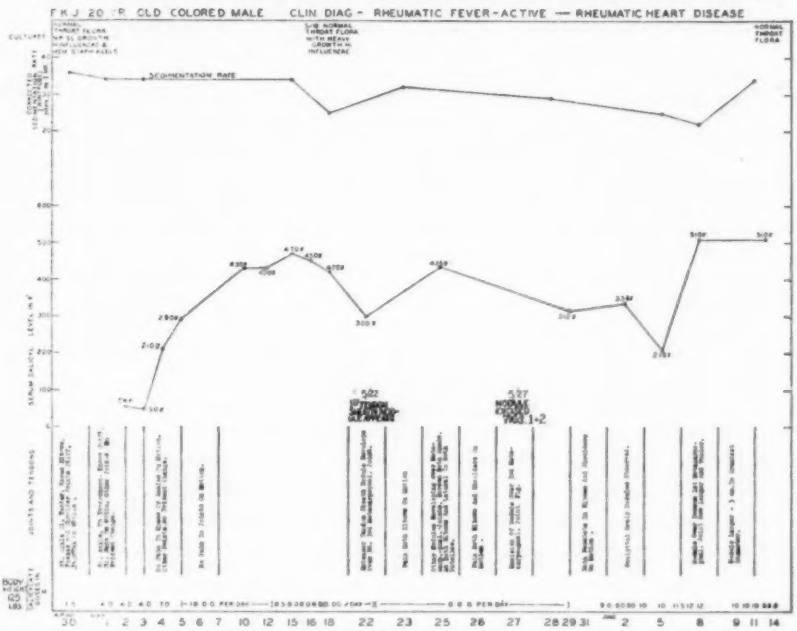
F.K.J. 20 yr. OLD COLORED MALE CLIN. DIAG. - RHEUMATIC FEVER-ACTIVE — RHEUMATIC HEART DISEASE
SEDIMENTATION RATE
SERUM SALICYL LEVEL IN MG%
JOINTS AND TENDONS
BODY WEIGHT IN LBS.
20 1 2 3 4 5 6 7 10 12 15 16 18 22 23 25 26 27 28 29 31 2 5 8 9 11 14

CHART 1

wrists, fingers, knees, and ankles. About 2 days later, he complained of a sore throat, and 2 days later, 3 days before admission, he had an epistaxis. On admission there was clinical evidence of mitral and aortic valvular disease. No tendon sheath or subcutaneous nodules were found in examinations by a number of observers on admission. The first 6 weeks of the patient's course on salicylate therapy may be followed in Chart 1.

In Chart 1 it may be seen that:

(1) Joint[3] pain recurred at a high serum salicyl level.

[3] Measurements of this patient's joints were not made.

TABLE IV

R. B., 14 Year Old Colored Male: Clin. Diag., Rheumatic Fever, Active

BODY WT. 92 LBS.		RIGHT ANKLE	LEFT ANKLE	LUNG FINDINGS	DIGITALIS	NA SALICYL. INTAKE	PLASMA SALICYL. LEVEL	RECTAL TEMP.	CORRECTED SEDIMENTAT. RATE (WINTROBE)
5/11/44	Size tend.	25.5 cm. ++	24.0 0	Few moist râles, both bases	.3 g.	7.5 g. (5.0 g. i.v.)		38.4°C.	21
5/12/44	Size tend.	25.5 +	24.0 0	Few moist râles, both bases	.3 g.	7.5 g.		38.4°C. ↓ 37.8°C.	
5/13/44				Coarse râles at bases		12.5 g.	320γ	37.8°C. ↓ 37.3°C. ↓ 38.0°C.	
5/14/44	Size tend.	25.0 0		Coarse râles, shifting character, patchy distribution, all lung fields	.2 g.	7.2 g.		38.0°C. ↓ 38.9°C.	
5/15/44				Râles diffusely throughout all lung fields		1.2 g.	420γ	38.9°C. ↓ 37.8°C.	

Autopsy

	TONSILS	PHARYNX	LUNGS	HEART	AORTA	ESOPHAGUS	KIDNEYS	BRAIN
Death 6:30 A.M. Autopsy —2:30 P.M.	Hyperplastic follicles Aschoff bodies peri-tonsillar connective tissue	Edema and alteration of collagen in sub-mucosa	Fibrin thrombi alveolar capillaries, occasional hyaline membranes, fluid, cells (chiefly polys) in alveolar spaces Bacterial stains negative (florid rheumatic pneumonitis, all lobes). Fig. 3	Fresh rheumatic pericarditis, myocarditis, tricuspid, mitral and aortic valvulitis	Edema and alteration of collagen in adventitia		Fresh fibrin thrombi in glomerular capillaries. Fig. 4	Peri-vascular round cell infiltration, vessels in cerebral cortex

(2) Rheumatic tendon sheath and scalp nodules began to appear on the 23rd day of treatment with salicylate (serum salicyl levels ranging between 300γ and 500γ per cc.). 4 days later the first tendon sheath nodule observed was excised[4] (Figs. 1 and 2).

(3) The corrected sedimentation rate remained above 25 during the 46 days of observation. From the 7th to the 46th day the serum salicyl levels remained between 300γ and 510γ except for a level of 210γ on the 37th day.

Case history 5: R. B., (hosp. no. 321082) a 15 year old colored boy was admitted to the Johns Hopkins Hospital on May 11, 1944, complaining of pain in the umbilical area and swollen ankles of 5 days' duration. In February, 1943, he experienced an attack of migratory joint pains involving the knees, ankles, toes, elbows, wrists, and finger joints. At bed rest the attack lasted 2 to 3 weeks. About one year before admission he had severe epistaxis, and since that time several more but milder bouts of epistaxis had occurred. About 4 weeks prior to this admission he became aware of "fever", and about the same time observed "hives" over both legs. 5 days before admission he developed steady, rather dull mid-abdominal pain, unrelated to eating. His ankles began to swell and he went to bed. 2 days before admission he became nauseated and vomited; the abdominal pain continued. The internal maleolar area of his right ankle became tender about 2 days before admission. There was evidence of myocardial, mitral and aortic valvular disease on admission. Examinations made for tendon sheath and other subcutaneous nodules failed to reveal their presence. The course of the patient may be followed in Table IV.

Table IV. It appeared that the florid rheumatic pneumonitis (Fig. 3) developed in this case during the course of salicylate therapy, with the plasma salicyl level above 300γ per cc. See also Fig. 4.

Case history 6: M. McC., (hosp. no. 241530) a 29 year old colored woman was admitted to the Johns Hopkins Hospital on February 12, 1945, complaining of a swollen, tender left wrist and right elbow, and tenderness over the 7th cervical vertebra. There was no previous history of rheumatic fever. About 4 weeks before admission the patient developed swelling with some tenderness of the left ankle (no history of an antecedent upper respiratory infection). About 1 week later the right knee became swollen and tender, and a few days later the left knee became involved. These joints had subsided symptomatically about 2 weeks after the first joint involvement. 4 to 5 days later the patient developed pain and swelling in the left shoulder and tenderness in the cervical spine followed in a few days by pain in both sternoclavicular joints. At this time the patient felt a

[4] Dr. Herbert Sloan excised the nodule.

tive (florid rheumatic pneumonitis, all lobes). Fig. 3

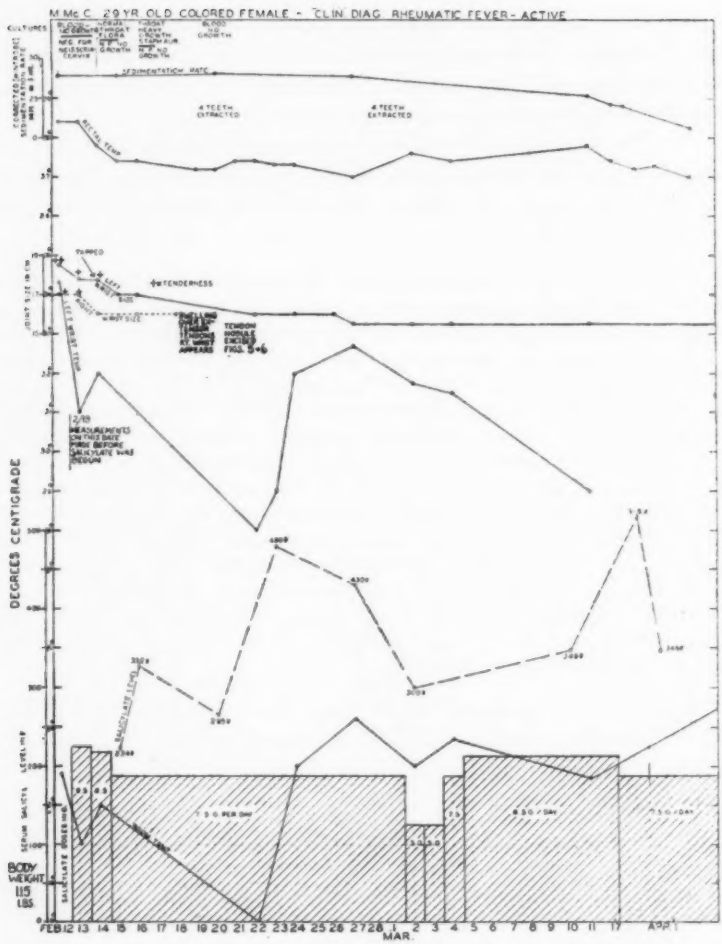
M Mc C 29 YR OLD COLORED FEMALE - CLIN DIAG RHEUMATIC FEVER - ACTIVE
SEDIMENTATION RATE
4 TEETH EXTRACTED
4 TEETH EXTRACTED
TENDERNESS
DEGREES CENTIGRADE
BODY WEIGHT 115 LBS
FEB 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 1 2 3 4 5 6 7 8 9 10 11 17 Apr 1
MAR.

CHART 2

marked subjective increase in body temperature. 3 days before admission the right elbow became swollen and tender and there was pain without swelling in the right wrist. The night before admission the left wrist became swollen and tender. On admission the dorsum of the left wrist and hand was swollen, quite warm and tender. An apical systolic murmur and rather marked low voltage in the limb leads of the electrocardiogram were the cardiac findings on admission. Aside

from the extensor tendon sheath involvement at the left wrist, no tendon sheath or subcutaneous nodules elsewhere were found on admission. The course of the patient on salicylate therapy may be followed in Chart 2.

From Chart 2 it may be seen:

(1) A sharp decrease in left wrist skin temperature before salicylate therapy was begun corresponded with a fall in room temperature (rectal temperature remaining elevated at 39.4°C.).

(2) An extensor tendon sheath swelling at the right wrist became apparent on the evening of the 8th day of salicylate therapy (serum salicyl level between 350γ and 265γ). On the following day this lesion was surgically explored,[5] found to be a swollen, rather tense extensor tendon sheath nodule (Fig. 5), and excised (Fig. 6).

(3) From this point on the serum salicyl level was maintained between 300γ and 500γ. The corrected sedimentation rate remained above 25 for 58 days of salicylate therapy.

Case history 7: E. T., (hosp. no. 344275) a 17 year old white male was admitted to the Johns Hopkins Hospital on February 20, 1945, complaining of "rheumatic" pains of 2 months duration. The patient stated that he had developed many sore throats until his tonsils were removed at 12 years. Since that time he had developed occasional sore throat which persisted for several days. On December 9, 1944 he experienced sharp pain in the right knee which forced him to bed. The following morning he awoke with pain in the left knee, pain in the right knee continuing. In a migratory fashion both ankles, shoulders, and finger joints became involved in the next few days. For about 10 days before admission there had been pain high in the cervical spine and in both shoulders. On admission stiffness of the left elbow was the only joint finding. There was clinical evidence of heart disease. It appeared grossly that there was infected lymphoid tissue in the left tonsillar fossa; B. hemolytic streptococci were not cultured in material from this tissue. No tendon sheath or other subcutaneous nodules were found on admission. By the morning of the 4th hospital day the patient had developed definite pain and tenderness in the right knee and ankle and left shoulder. Joint measurements were made before salicylate therapy was begun. The course of the patient may be followed in Chart 3.

In Chart 3 the following may be seen:

(1) An appreciable decrease in skin temperature of the right knee had occurred after 24 hours of salicylate therapy corresponding with a fall in rectal temperature from 38.3°C. to 37.6°C., but associated with a rise in room temperature.

[5] Dr. Oliver D. Forman excised the nodule.

(2) There was no measurable decrease in size of the right knee until the 5th day of salicylate therapy.

(3) Not until after the 3rd day of salicylate therapy was there an appreciable fall in skin temperature in the case of the left 1st metacarpo-phalangeal joint.

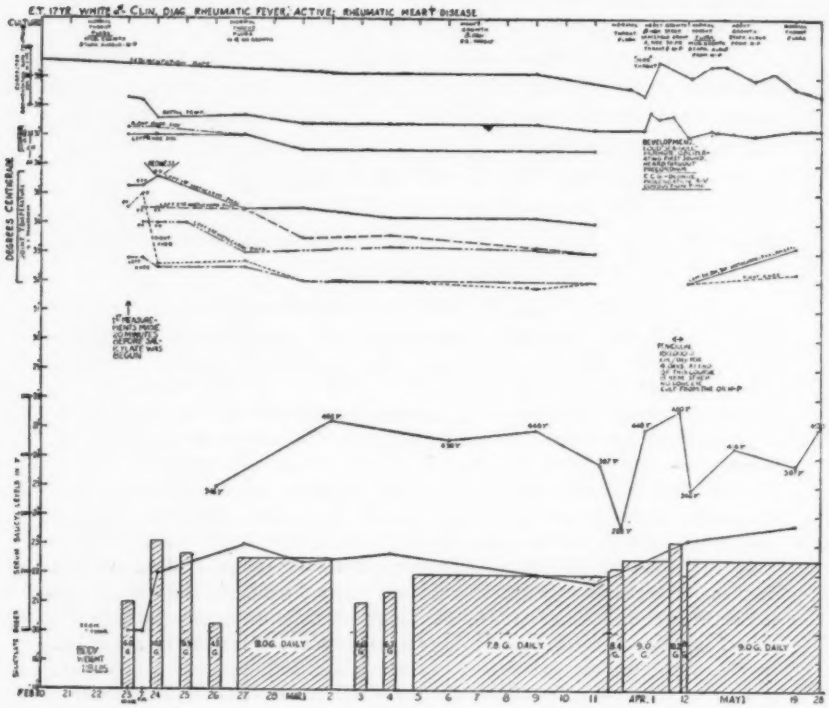

CHART 3

(4) A fall in skin temperature of the left 2nd metacarpo-phalangeal joint did not occur until after the 5th day of salicylate therapy.

(5) The skin temperature of the left 1st metacarpo-phalangeal remained elevated above that of the 2nd and 3rd metacarpo-phalangeal joints as long as the 17th day of salicylate.

(6) The corrected sedimentation rate remained above 20 for 15 days after the beginning of salicylate therapy.

Case history 8: G. S., (hosp. no. 343651) a 14 year old colored girl was admitted to the Johns Hopkins Hospital on February 9, 1945, complaining of a swollen, tender left knee and elbow. There was no past history of rheumatic fever. One month before admission the patient developed a cold and sore throat. 5 to 6 days later she began to have pain in the left knee. Swelling of the knee was noticed

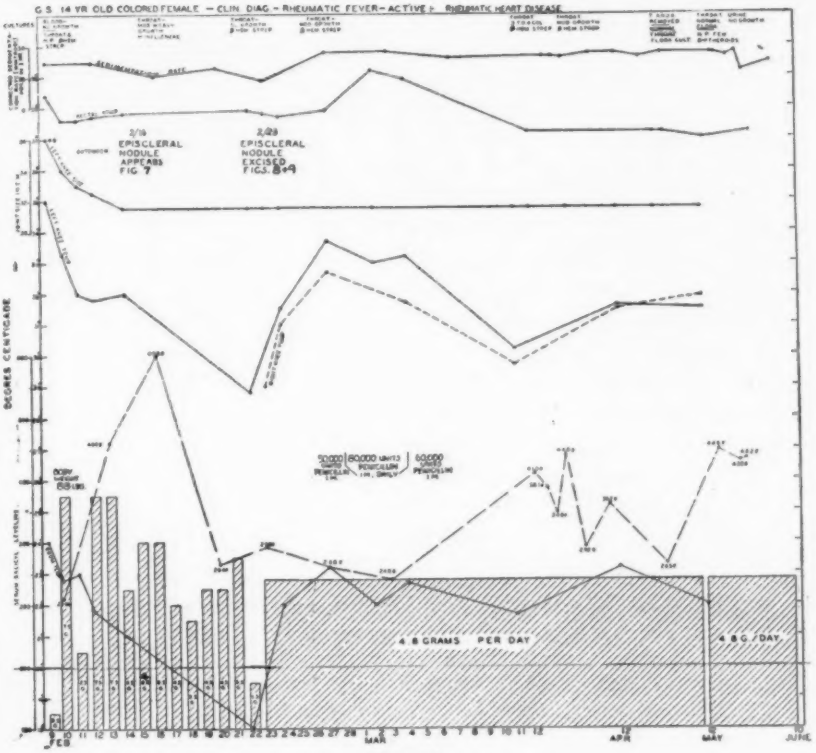

CHART 4

and pain in the left foot began about 2 weeks before admission. A few days later the knee pain was severe enough to prevent the patient from walking for 1 day. The knee began to show improvement (the patient felt) about 2 days before admission. On the day before admission the left elbow began to swell and became painful. In the hospital the tonsils and pharynx did not grossly appear to be infected. Clinical evidence of heart disease consisted chiefly of a harsh systolic murmur at the apex associated with the electrocardiographic findings of slight

notching of P_1, and definite prolongation of the A-V conduction time. An examination was made for subcutaneous nodules. None was found. The left knee was swollen, tender, and showed increased heat. The left elbow appeared slightly swollen and was tender. The course of the patient on salicylate therapy may be followed in Chart 4.

Chart 4 shows that:

(1) An appreciable decrease in temperature of the left knee within 24 hours of the start of salicylate therapy corresponded with a falling rectal temperature from 38.3°C. to 37.6°C. and with a fall in room temperature.

(2) A decrease in size of the left knee could be detected within 24 hours after salicylate therapy was begun (history of beginning improvement 2 days before hospital admission).

(3) On the 15th day of salicylate therapy skin temperature readings were begun on the apparently uninvolved right knee (the skin area corresponding to that being measured in the case of the involved knee). From this day to as late as the 48th day the skin temperature of the left knee remained above that of the right knee.

(4) On the 5th day of salicylate therapy (serum salicylate levels above 450γ) hyperemia of the bulbar conjunctiva of the left eye became apparent. On the 6th day (serum salicyl level between 450γ and 600γ) a yellowish white nodule became evident (Fig. 7), appearing to involve the bulbar conjunctival and episcleral tissue of the left eye.[6]

[6] Fernet (25) in 1865 reported the case of a 38 year old white woman in a recrudescence of clinically evident rheumatic fever "rhumatisme aigu" who developed 2 days following the onset of polyarthritis considerable tumefaction and hyperemia of the bulbar conjunctiva of first the right eye and within 24 hours the left eye as well which was reabsorbed in 6 days. Without reference to further specific evidence he concluded in his report of ocular involvement in "rhumatisme articulaire aigu" that: "Rheumatism can affect the conjunctiva and there occurs either a simple congestion, characterized by redness, or a development of papules and even vesicles, or a serous chemosis produced by the active edema of the submucous cellular tissue." Terrier (26) in 1884 reported the case of a 28 year old white woman with clinically evident "rheumatisme articulaire aigu" who developed, about 30 days after onset of polyarthritis, hyperemia and chemosis of the bulbar conjunctiva of the left eye with gradual reabsorption occurring within 1 month. In 1924 Rateau (27) described in the case of a 21 year old white male the occurrence of diffuse bilateral sclero-tenonitis ("scléro-ténonite rheumatismale") developing 2 days before onset of polyarthritis. The sclerotenonitis regressed in 4 days but 3 days

A narrow zone of hyperemia surrounded the nodule and the conjunctival epithelium overlying the lesion was ulcerated in at least 2 small areas. 9 days later the nodule was excised,[7] having decreased about 50% in size (Figs. 8 and 9).

(5) At the end of 112 days of salicylate therapy the corrected sedimentation rate remained above 25.

Case history 9: H. A., (hosp. no. 159250) an obese, 32 year old colored female was admitted to the Johns Hopkins Hospital on February 28, 1945, complaining

later recurred with moderate intensity, then rapidly reabsorbed in 2 days. More recently Babel (28) reported a clinical-histologic study of a case of unilateral sclero-tenonitis first developing in the course of a rheumatic recrudescence (in a 35 year old white male) and clearing within 4 weeks. 8 months later there developed in the case of the same eye enormous palpebral edema, considerable hyperemia of the conjunctiva and sclera and exophthalmus in association with outspoken signs of cardiac decompensation. 2 weeks later the patient expired as the eye affection was regressing. Histologic study of the heart revealed a healing rheumatic myocarditis and endocarditis. Low power photomicrographs of sections of the clinically involved eye show hyperemia and mononuclear perivascular infiltrates in the subconjunctival and episcleral tissue and in the choroid and ciliary body. A photomicrograph of higher magnification of a section of superior oblique muscle appears more convincingly to show a nodular adventitial collection of large mononuclear cells (appearing to the author under the microscope to closely resemble "les cellules décrites par Aschoff"). The author observed in further muscle sections cells of the rheumatic giant cell type about a vessel with edema and alteration of collagen in the vessel wall and between adjacent superior oblique muscle cells with necrosis of some of the latter. Marchesani's (29) excellent photomicrographs of sections of an eye from an acute rheumatic patient appear to clearly show rheumatic nodules and collections of large mononuclear, rheumatic type cells in the sclera and choroid (no clin. hist.). Fuchs (30) in writing of "episcleritis rheumatica" states: "A circumscribed inflammatory node develops in the sclera in this form. The diseased area is lifted up by the deposition of the exudate into a hump, sometimes flat, sometimes steep, of the size of a pea or over. It is permeated by violet, deeply-placed (episcleral) vessels and is immovably fixed to the sclera, whereas the conjunctiva over it is probably injected but is freely movable." He states that this lesion "appears to have a connection with rheumatic or gouty diseases in some cases." Duke-Elder (31) refers to "nodular episcleritis" and points out its usual association with rheumatic disease. Neither Fuchs nor Duke-Elder refer to histologic studies of these lesions. The author of the present paper has excluded from this review reference to ocular disease, notably scleromalacia perforans, associated with rheumatoid arthritis.

[7] Dr. William Owens excised the nodule.

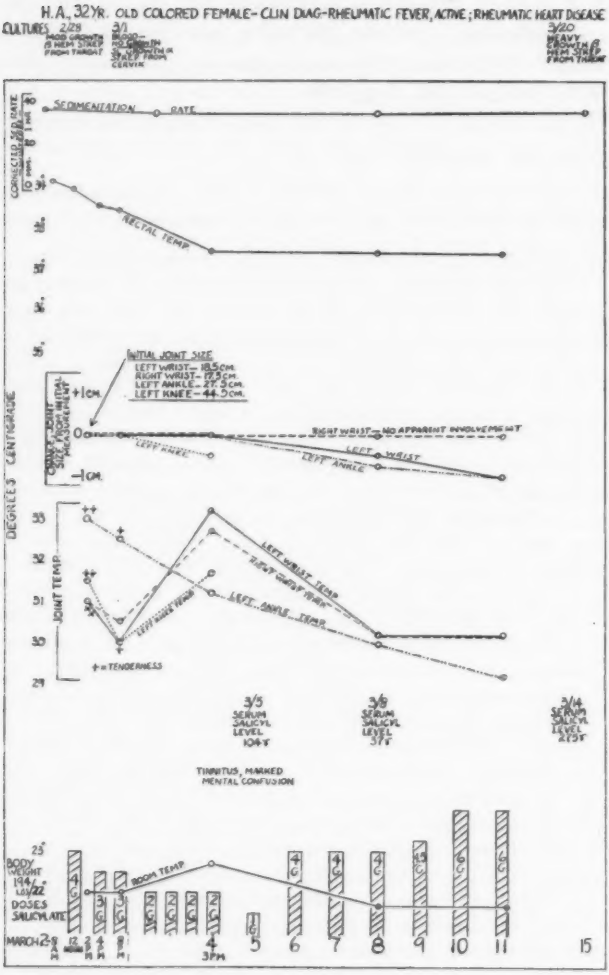

CHART 5

of pain in the left lower chest, increasing on deep inspiration. The patient was well until 3 weeks before admission when she developed a cold which soon passed, she felt, into her chest. There was no soreness of the throat. The cold persisted, and 4 days before admission the patient experienced shaking chills and became

feverish. Several hours later a continuous, dull pain began in the left chest, anteriorly and posteriorly. The night before admission the left chest pain became unbearable. On examination in the hospital the tonsils grossly appeared large and red. There was dullness to percussion of the left lower lung field, the breath sounds in this area being of a tubular quality. Moist râles were heard in this area. On admission a leathery to-and-fro friction rub could be heard in the 2nd and 3rd left interspaces, this finding being absent by the 2nd hospital day. The heart sounds on admission were practically inaudible except at the base where a rough systolic blow was heard. The pulse was palpably paradoxical (confirmed by a manometer—110–100/65). The left ankle was tender, appeared swollen and showed increased heat. Since it was thought on admission that the patient might have a blood stream infection, she received 8 gm. of sulfadiazine on February 28, and 4 gm. on March 1. By the morning of March 2 the left ankle had become more tender and the left knee and wrist had become tender for the first time. On this day an examination for subcutaneous nodules was made. None was found. Salicylate therapy was begun on March 2, 2 hours before the first joint measurements were taken. The course of the patient's joints during the first 15 days of salicylate therapy may be followed in Chart 5.

Chart 5 shows that:

(1) An appreciable decrease in skin temperature of the left ankle by the 3rd day of salicylate therapy corresponded with a fall in rectal temperature.

(2) A measurable decrease in size of the left ankle could not be detected until after the 3rd day of salicylate therapy.

(3) An appreciable fall in skin temperature of the involved left wrist and left ankle (corresponding with a fall in that of the apparently uninvolved right wrist and a slight fall in room temperature) was evident after 8 hours of salicylate therapy.

(4) A measurable decrease in size of the left knee was detected on the 3rd day of salicylate therapy.

(5) A measurable decrease in size of the left wrist was not detectable until after the 3rd day of salicylate therapy.

(6) The corrected sedimentation rate remained above 20 as late as the 47th day of salicylate.

Case history 10: J. F., (hosp. no. A-39399) an 11 year old white boy was admitted to the Harriet Lane Home, Johns Hopkins Hospital on March 25, 1945, complaining of tender, swollen right knees. There was no history of evident upper respiratory infection and no past history of rheumatic fever. 4 days prior, in the evening, he began to experience rather severe mid-abdominal pain which abated and recurred for about 48 hours. On the evening of March 23 he vomited. On

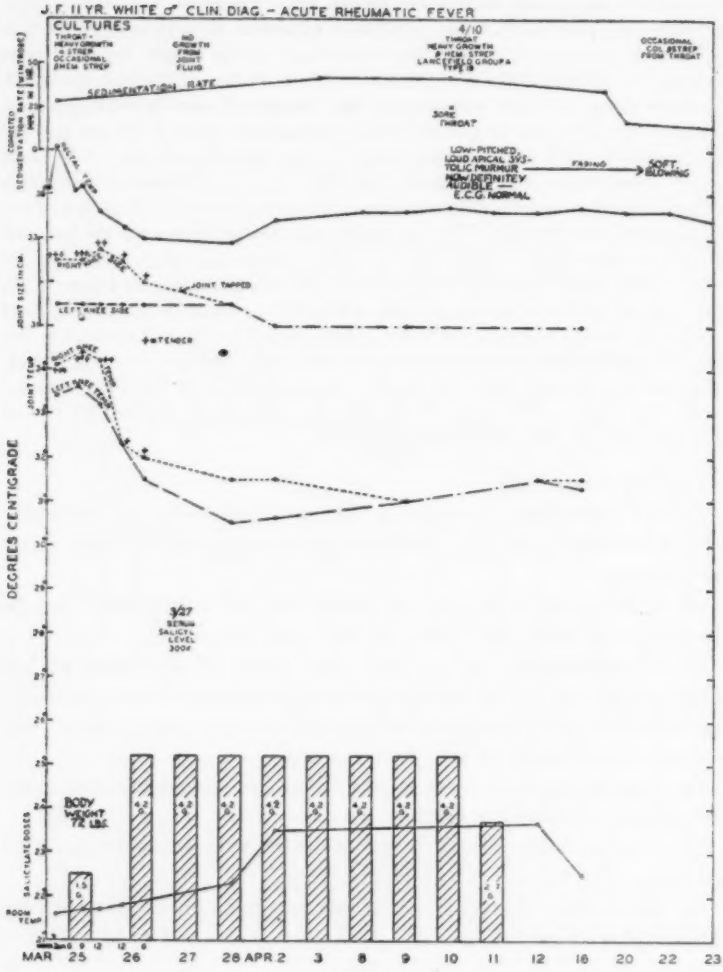
J. F. 11 YR. WHITE ♂ CLIN. DIAG. – ACUTE RHEUMATIC FEVER
CULTURES
SEDIMENTATION RATE
SORE THROAT
LOW-PITCHED, LOUD APICAL SYSTOLIC MURMUR NOW DEFINITELY AUDIBLE — E.C.G. NORMAL
FADING
SOFT, BLOWING
JOINT TAPPED
TENDER
3/27
SALICYL. LEVEL 300+
BODY WEIGHT 72 LBS.
DEGREES CENTIGRADE
MAR 25 26 27 28 APR 2 3 8 9 10 11 12 16 20 22 23

CHART 6

March 24 only slight right upper quadrant tenderness was elicited in the dispensary. The boy returned home and in the night he awoke, crying with pain in the right knee. On admission the right knee was swollen, painful, and quite tender. There was no abdominal pain or tenderness. Clinically the heart was

normal. No subcutaneous nodules were found on examination. The course of the patient on salicylate may be followed in Chart 6.

Chart 6 shows that:

(1) An appreciable decrease in skin temperature of the involved right knee after 20 hours of salicylate therapy corresponded with a fall in temperature of the clinically uninvolved left knee and rectal temperature.

(2) A measurable decrease in right knee size was evident after 26 hours of salicylate therapy.

(3) The skin temperature of the involved right knee remained above that of the clinically uninvolved left knee as late as the 16th day of salicylate therapy.

(4) The corrected sedimentation rate remained above 30 as late as the 24th day of salicylate therapy.

Case history 11: F. J., (hosp. no. 306423) a 16 year old colored girl was admitted to the Baltimore City Hospital on May 10, 1945, complaining of a tender, swollen right wrist and left index metacarpo-phalangeal joint. About 3½ years prior, the patient began to experience pains in the muscles of her legs, in her knees, and in her ankles. The joint pain was associated with swelling and tenderness. About 2 years prior to this admission dyspnea on exertion began to occur. In November, 1943, the patient was admitted to the Johns Hopkins Hospital because of increasing dyspnea and swelling of both ankles. There was at this time clinical evidence of mitral and aortic valvular disease. No tendon sheath or other subcutaneous nodules were found during a "careful search" by examiners at that time. There was no acute involvement of any joint. From January, 1944 until April 11, 1945 the patient was confined in turn in 2 rural hospitals near Baltimore, but was followed periodically in the Harriet Lane Cardiac Clinic of the Johns Hopkins Hospital, where the patient's corrected blood sedimentation rate was found to be above 30 on every examination during this time. For 4 to 5 months preceding the City Hospital admission the patient had suffered several bouts of epistaxis. About 10 weeks before this admission the left wrist began to swell, became tender and painful. In the following weeks the knees, ankles, and elbows became involved in a migratory fashion. About one week before admission the right wrist and left index metacarpo-phalangeal joints became swollen, tender, and painful. On the afternoon of the City Hospital admission the patient was seen first in the Harriet Lane Cardiac Clinic, where the last two above mentioned joints appeared acutely involved. The patient was examined by two observers for subcutaneous nodules but none was found. There was clinical evidence of mitral and aortic disease. On the day the patient was admitted to the City Hospital the medical interne in her examination likewise did not find any subcutaneous nodules. The

writer's customary examination for tendon sheath and other subcutaneous nodules was carried out the morning of May 11. No nodules were found. The course of the patient on salicylate therapy may be followed in Chart 7.

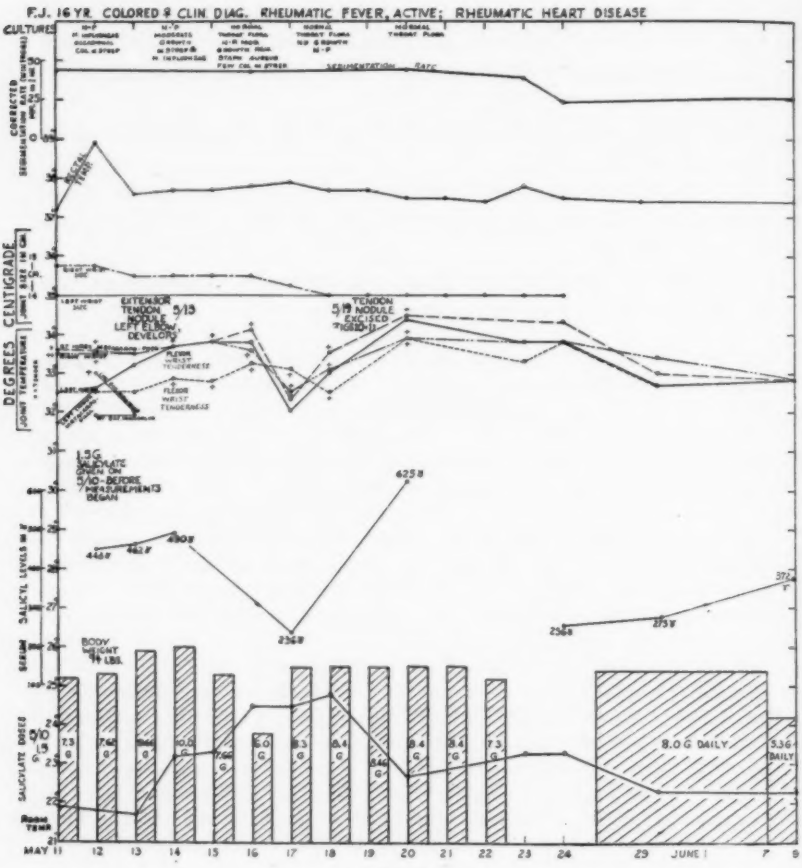
F.J. 16 YR. COLORED ♀ CLIN. DIAG. RHEUMATIC FEVER, ACTIVE; RHEUMATIC HEART DISEASE
CULTURES
SEDIMENTATION RATE
DEGREES CENTIGRADE
EXTENSOR TENDON NODULE LEFT ELBOW DEVELOPS
TENDON NODULE EXCISED
1.5 G. SALICYLATE GIVEN ON 5/10 - BEFORE MEASUREMENTS BEGAN
BODY WEIGHT IN LBS.
SALICYL DOSES
8.0 G DAILY
3.36 DAILY
MAY 11 12 13 14 15 16 17 18 19 20 21 22 23 24 29 JUNE 1 7 9

CHART 7

Chart 7 shows that:

(1) A measurable decrease in size of the right wrist was evident on the 4th day of salicylate therapy.

(2) After the 3rd day of salicylate therapy, in spite of a fall in

rectal and room temperature, the temperature of the left index metacarpo-phalangeal joint continued to rise.

(3) On the 4th day of salicylate therapy (serum salicyl level above 450γ per cc.) an extensor tendon sheath nodule at the left elbow measuring about 1 cm. in diameter which was not present on examination of this site 2 days previously. On the 7th day the nodule appeared to reach its maximal size of almost 2 cm. (on this day the cardiac rhythm was totally irregular). When, on the 10th day the nodule was excised,[8] it had decreased perceptibly in size (Figs. 10 and 11).

(4) On the 8th day a sharp fall in skin temperature of 3 involved joints (no appreciable concomitant change in room or rectal temperature) corresponded with a fall in serum salicylate to the lowest level (236γ) of this patient's study. 3 days later the skin temperature of all joints being followed showed an increase (room temperature fell, no change in rectal temperature) corresponding with an elevation of serum salicyl to the highest level (625γ) in this patient's study.

(5) The skin temperatures of the 4 joints were at the same level on the 30th day of salicylate.

Case history 12: B. B.,[9] (hosp. no. 100329) a 20 year old white Lansing, Mich.-born phm. 3/c underwent a submucous resection at the U. S. Naval hospital, Oakland, Calif. on June 29, 1945. On July 3rd he experienced bilateral frontal headache, chills and fever which was recorded as high as 102°F. By July 5th he was improved, complaining only of a feeling of malaise. On July 8th he complained of aching and dull pain in his arms and legs and lower back and was feverish. By July 11th he seemed enough improved to warrant return to duty at San Bruno, Calif. On July 12th he experienced several short bouts of substernal pain and on July 15th aching and dull pain in his left shoulder and arm and lower back. On admission to the Naval dispensary at San Bruno on July 16th a pericardial friction rub could be heard distinctly on auscultation. From this date the patient received in all 840,000 units of penicillin to July 20th, on which day he was readmitted to the U. S. Naval hospital, Oakland. There was auscultation and electrocardiographic evidence of pericarditis. There were on admission no signs or symptoms referable to joints. No subcutaneous nodules were evident. A T. & A. had been carried out in June, 1944 following a series of sore throats. At 7 years of age the patient's activities were restricted during the summer because of "heart trouble." In June of 1944 the patient had scarlet fever, apparently un-

[8] Dr. John McGee excised the nodule.

[9] The author appreciates the permission of Capt. A. M. Snell (MC) U.S.N.R. to study this patient. This study is not to be considered a part of the rheumatic fever program of the U.S.N.

complicated. The family history obtained was too scanty for evaluation as to rheumatic fever. The hospital course of the patient may be seen in Chart 8.

In Chart 8 it may be seen that: (1) Joint swelling, pain, and tenderness occurred for the first time after 15 days of heavy salicylate therapy. (2) Increased cardiac rheumatic activity (as indicated by the increase in A-V conduction time) appeared to be associated with joint rheumatic activity. (3) The sedimentation rate remained above 25 after 21 days of large doses of sodium salicylate.

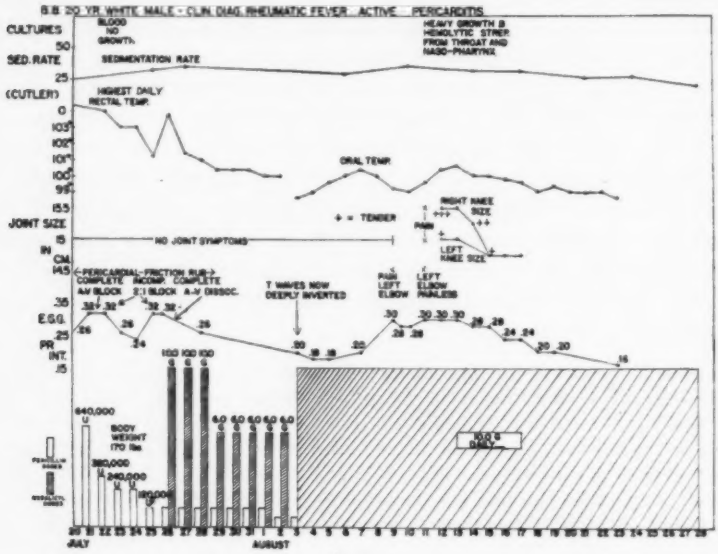

CHART 8

DISCUSSION

The purpose of this study was to attempt to determine by objective methods the effect of salicylate upon the development and course of superficially visible rheumatic lesions. The reason for this attempt was, that in spite of the widespread belief that salicylates bring about a rapid decrease in inflammatory edema and local heat of the rheumatic joints and may *prevent* the development of the rheumatic lesions, the writer was unable to find any report in the literature in which this point had been actually studied by objective methods.

A breakdown of the data referable to the course of joint size and skin temperature over the affected joints in the present study reveals that

of the 24 joints measured for size under salicylate therapy, 4 had decreased before salicylate was begun, 2 decreased within 24 hours, 3 showed a measurable decrease within 48 hours, 6 showed a measurable decrease in between 48 hours and 5 days, in 2 joints there was no measurable decrease before 5 to 8 days, and 5 joints showed no change in size during the period of study (21 days). 2 joints became involved for the first time 15 days after the beginning of salicylate therapy. Of 15 joints, the skin temperature of which was followed, 1 showed a decrease in 8 hours, corresponding with a fall in rectal and room temperatures, 4 showed a decrease within 48 hours, corresponding in 2 cases with a decrease in both room and rectal temperature and in the other 2 with a decrease in rectal temperature only. The skin temperature of 5 joints showed a decrease in from 3 to 7 days, corresponding with a decrease in rectal temperature. 1 joint showed a sharp decrease in temperature before salicylate was begun corresponding with a fall in room temperature. 1 joint showed an increase on the 5th day of salicylate therapy in spite of a decrease in rectal and room temperature. The relief of pain in these patients on salicylate therapy occurred in most cases with the usual promptness. In the majority, however, there was no dramatic improvement in the measured size or temperature of the affected joints.

Indeed in the case of 4 joints on which 2 sets or more of daily measurements were made before salicylate therapy was begun, the rate of improvement after salicylate was no more rapid than that which was occurring before. Furthermore, typical rheumatic tendon sheath nodules (Figs. 1, 2, 10, 11) appeared for the first time under salicylate therapy in 2 cases (serum salicyl levels above 300γ and 450γ per cc. respectively). A florid rheumatic pneumonitis (Fig. 3) appeared to develop in 1 case with the serum salicyl level above 300γ, associated with the finding at autopsy of fresh fibrin thrombi in the capillaries of practically every glomulus in sections of both kidneys (Fig. 4). In 1 case a tenosynovitis (Figs. 5 and 6) developed with the serum salicyl level between 350γ and 265γ. In 1 patient an episcleral nodule (Figs. 7, 8, 9) developed (serum salicyl level between 450γ and 600γ per cc.).

Swift (32) is of the opinion that there are two types of tissue response in rheumatic fever, viz., (1) a "perivascular proliferative type of lesion, resembling an infectious granuloma" [he has observed the de-

velopment of subcutaneous nodules (33) (a tissue response considered by him to be of the proliferative type) in patients under the full therapeutic effect of salicylate]; (2) an exudative type of response in which there occurs "marked exudation of serum into the periarticular tissues and of serum and cells into the joint cavities." He is of the opinion that the reabsorption of these exudations appear to be related to the administration of fully therapeutic doses of salicylate. Many investigators are of the opinion that beginning rheumatic involvement in other joints regresses without running its natural course and no new joints are attacked during the course of fully therapeutic doses of salicylate.

The histologic findings in the more outspokenly exudative lesions (Figs. 1, 3, 5, 8, 9, 10) developing in the actively rheumatic patients receiving large doses of salicylate in the present study together with the outspoken development in the 12th patient of the present study of marked joint exudation for the first time after 15 days of large doses of salicylate are very difficult to reconcile with the opinions of the many investigators who feel that salicylate effects a reabsorption of rheumatic inflammatory exudate or subsidence of rheumatic activity. The present study was interrupted by the writer's entry into active military service. It is realized that the number of cases studied (twelve) is small. In future investigations of the claims so widely made for the effect of salicylate upon lesions of rheumatic fever, it will be particularly important to study the joints by objective measurement for a period *before* instituting salicylate therapy. The necessity for this is indicated by cases 1 and 6 of the present study. For one must bear in mind that spontaneous ebb and flow of activity is characteristic of rheumatic disease.

SUMMARY

An objective study of the clinical course and histologic character of rheumatic lesions in 12 actively rheumatic patients treated with large doses of salicylate was carried out. In 6 patients the size of involved joints and in 6 patients size and skin temperature of involved joints were followed by direct measurement in an attempt to determine the effect of salicylate upon the local rheumatic inflammation. The results in this small series of cases do not support the widely

accepted view that salicylate promotes the subsidence of the rheumatic joint inflammation. In several of these patients characteristic rheumatic lesions developed in a variety of sites during the course of salicylate therapy. In 2 cases tendon sheath nodules developed with serum salicyl levels above 300γ and 450γ per cc. respectively. In another case a tenosynovitis developed with the serum salicyl level between 350γ and 265γ per cc. A florid rheumatic pneumonitis appeared to develop in a fatal case with the serum salicyl level above 300γ per cc., another striking finding at autopsy in this case being fresh fibrin thrombi in capillaries of practically every glomerulus in sections of both kidneys. In a 5th patient an episcleral nodule developed with the serum salicyl level between 450γ and 600γ per cc. The histology of these lesions is illustrated and described. A review of the literature pertaining to episcleral and scleral lesions developing in the course of active rheumatic fever and evidence for considering the episcleral lesion in the present studies of rheumatic nature are presented. In a 6th patient joint rheumatic activity became manifest for the first time during the course of heavy salicylate therapy (after 15 days of large doses of salicylate) associated with electrocardiographic evidence of increased cardiac rheumatic activity.

The writer is greatly indebted to Dr. Arnold R. Rich for his encouragement and criticism throughout this study and to Dr. Homer F. Swift and Dr. Warfield T. Longcope for their interest and advice.

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EXPLANATION OF ILLUSTRATIONS

(Photographs by Miss Violet Crane, Miss Ruth Cordish, and Miss Betty Cone)

FIG. 1. TENDON SHEATH NODULE FROM CASE 4

At the left there is stringy, fibrinoid, degenerated collagen separated by oedema. Though this suggests fibrin in the photograph, it is clearly altered collagen under the microscope.

FIG. 2. ANOTHER AREA FROM THE NODULE SHOWN IN FIG. 1

There is a center of degenerated collagen (A) surrounded by mononuclear cells.

FIG. 3. RHEUMATIC PNEUMONITIS IN CASE 5

Note the fibrin thrombi in alveolar capillaries (phosphotungstic acid—hematoxylin stain). There is scanty leucocytic exudate, hemorrhage, and occasional hyaline alveolar membranes in the sections. No growth from the lungs on culture. No bacteria stainable in several sections.

FIG. 4. SECTION OF KIDNEY IN CASE 5

(Phosphotungstic acid—hematoxylin stain.) Fibrin thrombi in glomerular capillaries. Practically every glomerulus in kidney sections contained capillaries with fibrin thrombi.

FIG. 5. Line drawing (by Miss Ranice Birch) illustrating the bulging extensor tendon sheath in case 6.

FIG. 6. SECTION OF LESION ILLUSTRATED IN FIG. 5

At the left there is an exudate containing fibrin and a few leucocytes in the synovial cavity. The tissues beneath the synovial membrane show a mononuclear and polymorphonuclear exudate.

FIG. 7. PHOTOGRAPH OF EPISCLERAL NODULE IN CASE 8

FIG. 8. SECTION OF NODULE ILLUSTRATED IN FIG. 7

Between the perivascular collections of mononuclear cells greatly altered collagen may be seen in contrast to the normal wavy collagen in the upper right hand corner. Just above and to the right of the most altered collagen many red cells are seen without the confines of a vessel wall. Edema separating collagen is seen in the upper left hand corner and lower portion of photograph.

FIG. 9. HIGHER MAGNIFICATION OF AREA OF NODULE SEEN IN FIG. 8 (MALLORY'S ANILINE BLUE STAIN FOR COLLAGEN)

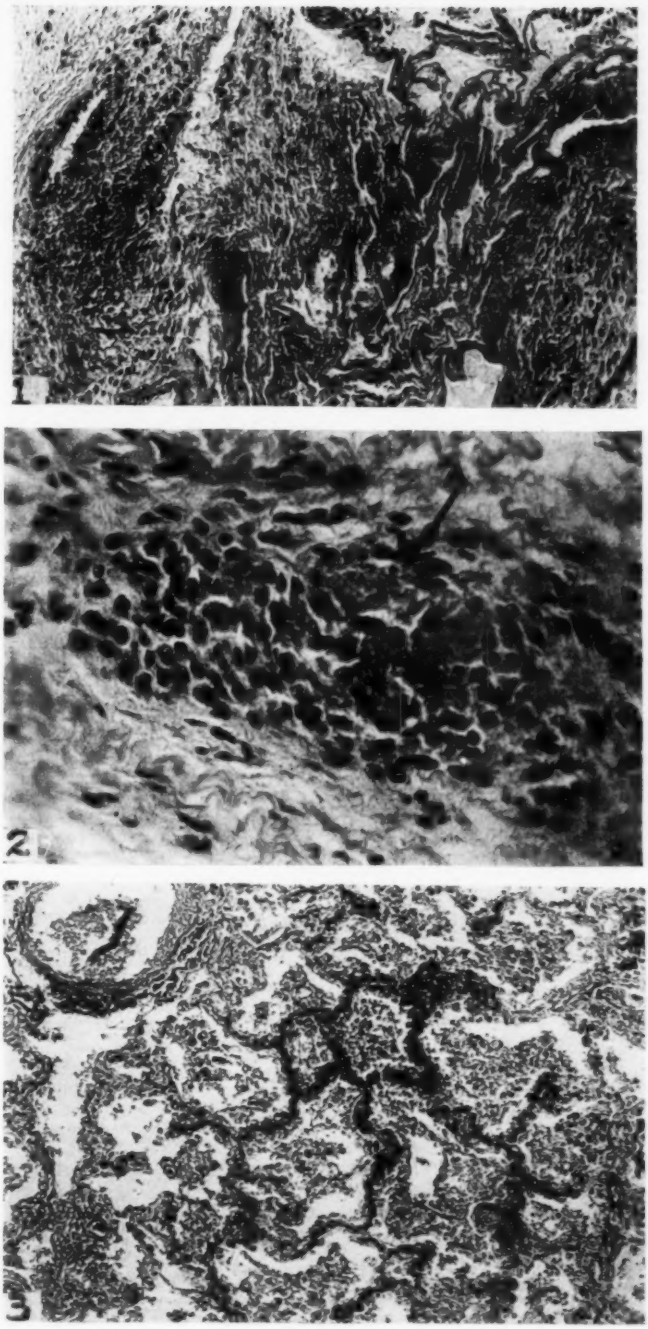
Altered collagen is more clearly evident in the center of the field. A—point of arrow is in the collection of red cells without vessel walls.

FIG. 10. EXTENSOR TENDON SHEATH NODULE IN CASE 11

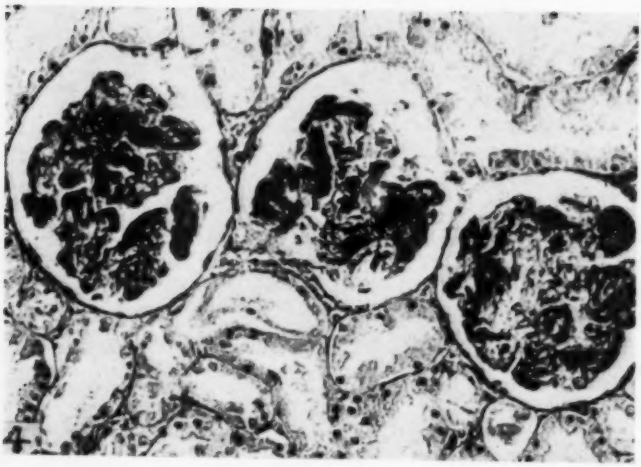
An area of greatly altered collagen and edema is bordered by a characteristic palisade of mononuclear and connective tissue cells.

FIG. 11. ANOTHER AREA IN THE NODULE OF FIG. 10

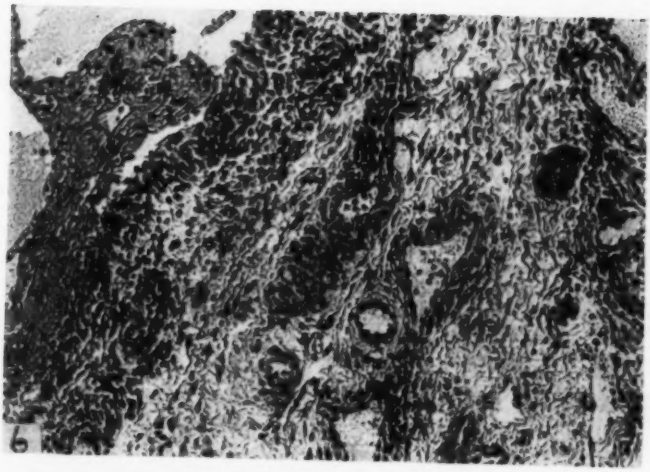
In the center is seen a focus of greatly damaged collagen.

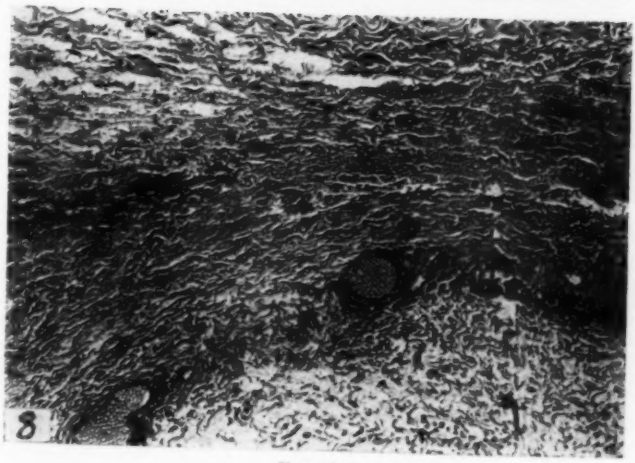


FIGS. 1–3

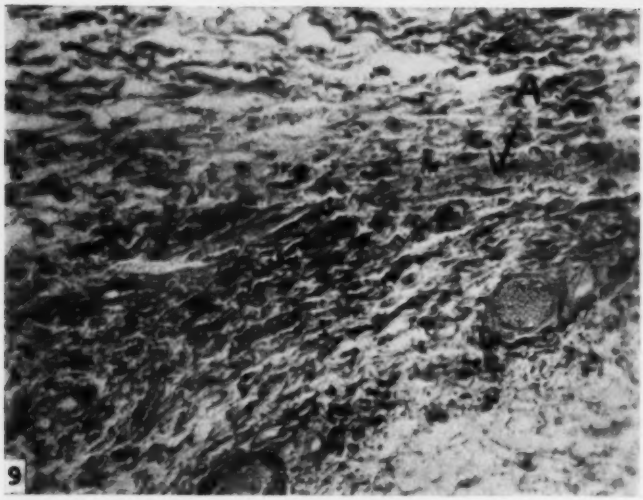


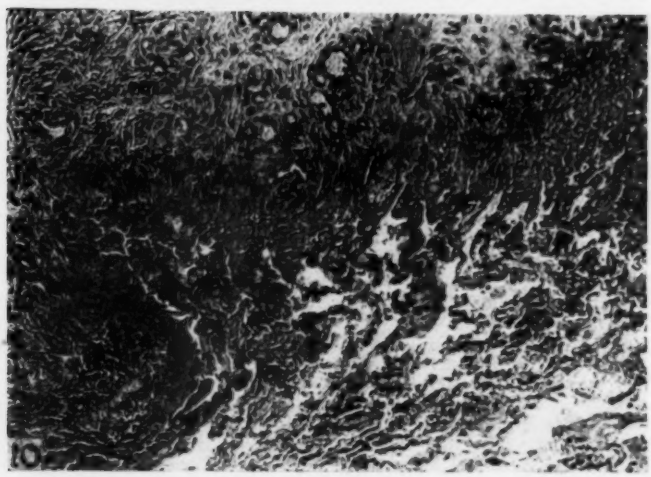
FIGS. 4–5

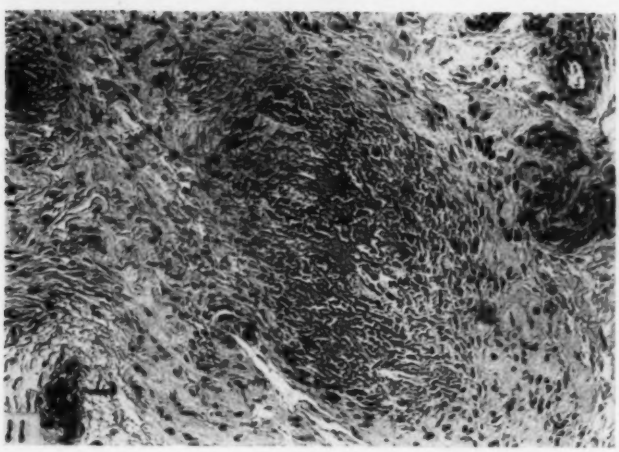




FIGS. 6–8







FIGS. 9–11

HYPERSENSITIVITY TO IODINE AS A CAUSE OF PERIARTERITIS NODOSA

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The writer has shown that the serum-sickness type of protracted, anaphylactic hypersensitive reaction to foreign serum and to sulfonamides can cause periarteritis nodosa in man (1) (2), and, with Dr. John E. Gregory, has demonstrated experimentally that this type of hypersensitive reaction can produce periarteritis nodosa in animals (3). The studies of Landsteiner (4) and of others have shown that if a non-antigenic chemical substance be united to a protein it then becomes able to stimulate the formation of antibody that reacts specifically with the chemical substance itself. This discovery provided a clue for the understanding of the mechanism by means of which non-antigenic drugs become able to sensitize the body, as they so often do; for in order that such drugs may become able to stimulate the formation of sensitizing antibody, it is necessary only that they have the capacity of uniting readily with plasma protein. The drug-protein complex will then act as a foreign protein to stimulate the formation of an antibody that will react specifically with the drug, even in the latter's free state; and a hypersensitive reaction will occur when the drug and the antibody meet, under suitable conditions, in the tissues.

In the case of the sulfonamides, it has been shown by Schönholzer (5) and by Davis (6) that these drugs do attach themselves readily to human plasma protein, thus satisfying the condition necessary for rendering them capable of stimulating the production of specific, sensitizing antibody. Since, by this mechanism, the sulfonamides become able to sensitize and, therefore, as we have shown, able to cause periarteritis nodosa, it may be expected that periarteritis nodosa will also result from hypersensitive reactions arising from a similar sensitization of the body to other drugs and chemical substances. From the standpoint of the etiology of the many "spontaneous" cases of periarteritis nodosa it is important to place on record every instance of this condition in which the sensitizing agent has been identi-

fied. The present report deals with an instance of periarteritis nodosa in which iodine was the offending, sensitizing agent.

It is well known that some patients under treatment with iodine develop hypersensitivity to this element. Not only do cutaneous eruptions of varying degrees of severity appear, but Barker and Wood (7) have described cases with additional manifestations of the serum-sickness type of hypersensitivity (fever, arthralgia, lymph node enlargement, eosinophilia). The studies of Friedberger and Ito (8) and of Jacobs (9) have shown that guinea pigs can be anaphylactically sensitized by a mixture of iodine and guinea pig serum. It appears, therefore, that, as in the case of the sulfonamides, iodine can attach itself to plasma protein and thereby become able to stimulate the formation of specific, sensitizing antibody.

CASE REPORT

B. B., (History No. U-45883), a 56 year old colored male, was admitted to the Medical Service of the Johns Hopkins Hospital complaining of nervousness, weakness and rapid heart, symptoms that began following an attack of influenza six months before admission. Three months before admission he noticed swelling of his ankles. Three weeks before admission he began to have moderate diarrhoea. He had lost 40 lbs. in weight since the onset of his symptoms.

His temperature was 98.6°F., pulse 130, respiratory rate 25 and blood pressure 180/80. There was a marked tremor. The eyes were prominent, with lid lag and weakness of convergence. Perspiration was profuse. The thyroid was diffusely enlarged, with a thrill and bruit. The basal metabolic rate was +66. The heart was somewhat enlarged; its rhythm was regular. There was an apical systolic murmur. The liver, spleen and superficial lymph nodes were not enlarged. The blood count was essentially normal. There was no eosinophilia. The Wassermann reaction was negative.

After a period of nineteen days of bed rest, with a high caloric diet and sedatives, treatment with compound solution of iodine (Lugol's solution), 3 cc. a day, was begun. Two days later the temperature was 101.2°F. The dosage of Lugol's solution was doubled. On the 5th day the temperature reached 103°F., and the patient complained of itching. Four days later the basal metabolic rate had dropped to +32 and the leucocyte count was 9,700, with 65 per cent polymorphonuclear leucocytes, of which 11 per cent were eosinophils. Because of the fever and eosinophilia, Lugol's solution was discontinued, and a saturated solution of potassium iodide, 1 cc. three times a day, was substituted in the hope that it would be better tolerated. The next day the temperature rose to 104.2°F., and the patient developed a dense, papular rash with papules 2–4 mm. in diameter. Marked coryza developed; the pharynx became fiery red; and hemorrhages ap-

peared in the buccal and palatal mucosae. The joints became painful. After two days of treatment with potassium iodide the patient's condition was so bad that the drug was discontinued. The temperature reached 104.8°F. The leucocyte count was 12,300, with 22 per cent eosinophils. Blood cultures were sterile. The patient became irrational and stuporous, and died three weeks after the beginning of iodine medication.

At autopsy (No. 12880), the pertinent gross findings were a generalized, desquamating, maculopapular rash; marked hyperemia of the larynx, trachea and

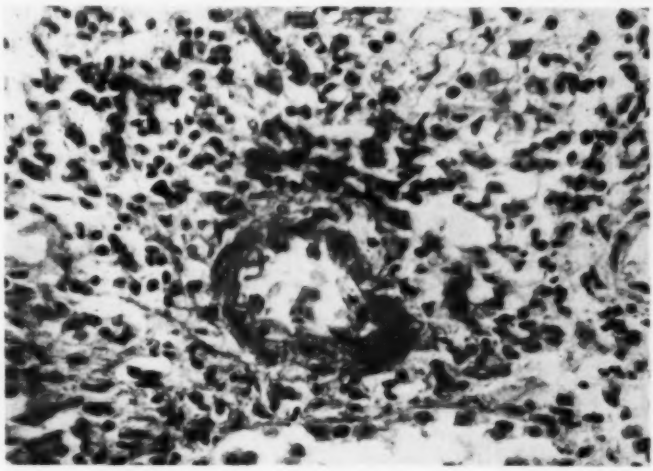

FIG. 1. ARTERY IN KIDNEY, SHOWING NECROSIS OF SEGMENT OF THE WALL

The perivascular cells are mononuclears and eosinophils. The wall of a renal tubule is below.

bronchi; enlargement of the thyroid and thymus; marked, generalized enlargement of the lymph nodes; enlargement of the spleen (wt. 370 gms.).

Microscopically, lesions characteristic of periarteritis nodosa were present in the kidneys, liver, testis, prostate, pancreas and spleen. The lesions consisted in smudgy or hyaline necrosis of the media of a segment, or of the entire circumference, of the artery, with perivascular infiltration of mononuclear leucocytes and eosinophils (Fig. 1). For the most part the vessels affected were small arteries. When larger arteries were involved, subintimal inflammatory infiltrations were also present.

In the spleen there were foci of coagulative necrosis, particularly beneath the capsule. These we have seen in the spleen and lymph nodes in other cases of periarteritis nodosa (1), and it is interesting that they occur in lupus erythema-

tosus, also (11). There was a smudgy degeneration of the collagen of some of the trabeculae of the spleen in the present case. In addition to these alterations and to the lesions of periarteritis nodosa, there were, in various tissues, focal infiltrations of eosinophils and mononuclear cells, and focal accumulations of epithelioid and giant cells which, in the spleen, were often about a center of degenerated collagen. Most, if not all, of these focal cellular infiltrations were adjacent to, or surrounding, small arteries. These perivascular infiltrations were present about some of the vasa vasorum in the media of the aorta. Ophüls (10) has described perivascular granulomata in periarteritis nodosa, and we have observed them in other cases (Autopsy Nos. 17805, 17895).

The thyroid gland showed marked hyperplasia, with some areas of involution in which more colloid was present and the acinar cells less hyperplastic.

DISCUSSION

We have shown in previous reports that, in the human being, periarteritis nodosa can result from hypersensitive reactions of the protracted and anaphylactic type caused by foreign protein or by sulfonamides (1) (2), and we have demonstrated experimentally that this destructive vascular lesion can be produced in animals by the same type of hypersensitive reaction (3). The present case shows that hypersensitivity to iodine, as well as to sulfonamides and to foreign protein, can cause periarteritis nodosa. These observations clearly indicate that a wide variety of different drugs and chemical substances may produce the lesion, depending upon their intrinsic antigenicity, or upon their ability to become antigenic by uniting with plasma protein after they enter the body, according to the principles mentioned in the introduction to this paper.

Why only some of the individuals who are exposed to these substances develop manifestations of hypersensitivity is at present as obscure as why only some of the individuals treated with foreign serum and sensitized by it develop serum sickness; or why only some of the persons exposed to pollens and sensitized to them develop asthma or hay fever. Why only some of those who exhibit other manifestations of hypersensitivity to drugs or foreign serum (e.g., fever, cutaneous eruptions, arthralgia) develop periarteritis nodosa, is as obscure as why different individuals sensitized to an identical antigen, such as egg protein, develop, following the ingestion of the antigen, such different manifestations of hypersensitivity as urticaria, eczema, purpura, a gastro-intestinal crisis, arthritis, or an asthmatic

attack. It is clear that there is a native, individual difference in reactivity which determines not only whether a given sensitized individual will, on contact with the antigen, develop a hypersensitive reaction, but also determines the character of the reaction, and in what tissue it will occur; but the nature of this individual factor is not yet understood.

It is of interest that in this patient, sensitized to iodine and exhibiting widespread vascular damage resulting from the continued introduction of iodine, the epithelial cells of the thyroid gland, which were overactive in the production of the iodine-containing hormone, and which avidly take in iodine under that circumstance, were entirely unharmed. This provides additional and striking evidence that in anaphylactic hypersensitivity the cells that will be killed as a *direct* result of contact with the antigen are those of the cardio-vascular system, in contrast to the more generalized sensitivity that is characteristic of the "tuberculin type" of hypersensitivity (12).

The demonstration that such widely different sensitizing agents as foreign serum, the sulfonamides and iodine can cause periarteritis nodosa renders it altogether probable that anaphylactic hypersensitivity to the products of bacteria or fungi, or, indeed, to certain foods, may be responsible for some cases of this vascular disease. It is important to make a careful search in the effort to discover the sensitizing antigen in every case of periarteritis nodosa that comes under clinical observation, for if it can be identified, the vascular damage could be stopped either by removing the source of the antigen, or by desensitization. Recovery will, of course, depend upon the abolition of free antigen from the blood stream before irreparable injury to vital processes has occurred.

SUMMARY

Our previous studies have demonstrated that anaphylactic hypersensitivity to foreign serum and to sulfonamides can cause periarteritis nodosa. The present report adds iodine to the sensitizing substances that can cause this destructive vascular lesion, and emphasizes that substances of widely different chemical nature have this potentiality, depending upon their ability to induce the state of anaphylactic hypersensitivity.

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POLIOMYELITIC CHANGES IN MULTINUCLEATED NEURONS, WITH SPECIAL REFERENCE TO THE SITE OF ACTION OF VIRUS IN THE CELL[1]

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The occasional occurrence of binucleated cells in some tissues has generally been interpreted as an accidental failure of the cell to divide following nuclear division. Such binucleated cells have often been observed in sympathetic ganglia, but not in other parts of the nervous system. It was surprising, therefore, to find considerable numbers of multinucleated neurons in various regions of the central nervous system of an adolescent rhesus monkey. This large and vigorous animal (A924) had received an intracerebral inoculation of poliomyelitis virus on August 30, 1944 and sustained a mild paralytic attack on September 18. Weakness was observed only in the right arm, which was reduced in power to about 80% of normal. Since no progress of paralysis was noted by September 20, he was killed for histological study by exsanguination under ether anaesthesia, and 1 liter of 10% formol containing 1% acetic acid was perfused intravascularly. No abnormality was suspected, so that only the brain, spinal cord and spinal ganglia were saved for routine examination.

Of particular interest was the fact that numerous multinucleated anterior horn cells were present in the spinal cord, and that many of these cells exhibited the degenerative changes characteristic of poliomyelitis. All stages of the pathological reaction of virus with neuron were represented in multinucleated as well as in ordinary motoneurons. Since cells containing nuclei varying in number from two to six were found, it became possible to make unique observations on the rôle of the nucleus in the virus-neuron reaction, studying groups of nuclei in a constant cytoplasmic environment.

Frequency and Characteristics of Multinucleated Neurons

Although multinucleated neurons were found in the brain-stem as well as in the spinal cord, only observations on poliomyelitic changes

[1]Aided by a grant from The National Foundation for Infantile Paralysis, Inc.

in anterior horn cells will be described because of their greater numbers, and because very few multinucleated cells in other sites exhibited obvious poliomyelitic effects. The frequency of occurrence of multinucleated anterior horn cells was about 4% in the lumbar enlargement, and about 1.5% in the cervical enlargement, estimated from 1180 15 μ sections examined. 213 multinucleated cells were found in a total of about 15,000 cells which had survived the acute stage of poliomyelitis. Of these multinucleated cells 159 were binucleated, 35 had three nuclei, 11 had four nuclei, 6 had five nuclei, and 2 had six nuclei. Multinucleated cells varied from normal to more than twice normal size, but axon diameters, measured in reduced silver preparations, were in the normal range. Some cells were of bizarre shape, and a few of the largest were vacuolated. Their nuclei varied from normal to one-half normal diameter. Several nuclei could be seen packed into a small cell in some cases, but in larger cells were often well spaced. Nuclei were normal in appearance except in cells which showed changes due to poliomyelitis. These findings and the fact that the Nissl bodies in cells which showed no characteristic changes of poliomyelitis were normal in appearance, indicate that the multinucleated neurons probably functioned as normal cells.

Poliomyelitic Changes in Multinucleated Cells

Multinucleated anterior horn cells exhibited poliomyelitic effects which were in no way different from those seen in ordinary neurons. In general such changes in the acute stage of poliomyelitis follow a definite sequence of morphological degenerative stages. A certain amount of variability from animal to animal is encountered, depending on the severity of the disease and other factors which will be considered in greater detail in a future publication. Earliest changes in gallocyanin and in haematoxylin-eosin-azure preparations in A924 were seen in the cytoplasm and consisted of chromatolytic changes of the cytoplasmic nucleoprotein, or Nissl substance (figs. 3 to 11; compare with normal cells, figs. 1 and 2). This degradation of chromophilic material had progressed in some cells to complete loss of this substance (fig. 11). Nuclei in cells with mild degrees of chromatolysis showed no cytological changes as a rule (figs. 3 to 5). However, when the breakdown and dispersion of Nissl bodies was well under way, a

progressive clumping of the normally irregularly disposed oxychromatin net was usually seen.

The clumping of oxychromatin in most cells seemed to lead to the formation of small and roughly spherical eosinophilic inclusion bodies (figs. 6 to 11). These were usually found in cells exhibiting severe chromatolysis, and were variable in size and number. In some cases only one or two of such masses, almost the size of the basophilic nucleolus, were found. In such instances it was remarkable that the nuclei of multinucleated cells each contained eosinophilic bodies of the same size and number (figs. 8 to 11). The nucleolus and nuclear membrane showed little, if any, morphological change until the cells had reached the point of presumed necrosis, although nucleolar displacement away from the center of the nucleus seemed to be common in earlier stages (figs. 6 to 11). In cells which showed complete loss of stainable Nissl substance it was common to see more sharply stained nuclear membranes, varying degrees of nuclear shrinkage, small basophilic masses in the nuclei, nucleolar fragmentation, nuclei of crumpled appearance, and sometimes nuclear as well as cellular "ghosts" (figs. 12 to 14). All of these changes are probably in the range of irreversible cell injury, or necrosis.

Although the foregoing description of cellular and nuclear changes due to poliomyelitis is by no means complete, it serves to give a background for the most striking finding in poliomyelitic multinucleated cells. This was the fact that all nuclei in any single multinucleated motoneuron were almost identical in appearance, regardless of the stage of degeneration of cell or of nuclei. This is best illustrated by the photomicrographs shown in figures 3 to 14 of selected cells with various degrees of poliomyelitic change. Only in the final stages of cell injury were differences present in the nuclei of a single multinucleated cell. This is not surprising since one might expect greater variation at a stage where cellular mechanisms are quite out of control. As can be seen in figures 12 to 14, even the differences at the stages of severest cell change were minimal.

DISCUSSION

The finding that all the nuclei in a single multinucleated cell are invariably identical, or almost identical, in appearance, regardless

of the degree of poliomyelitic change, is sufficiently unusual to call for an attempt at interpretation. As alternative hypotheses regarding the site of virus action in the nerve cell one may suppose that the virus reacts either with nuclear mechanisms alone, with cytoplasmic mechanisms alone, or with both. If the primary reaction of virus within the cell were in the nucleus it seems improbable that all nuclei in the same cell would invariably be involved simultaneously and to the same degree. For example, the uniformity of response of groups of nuclei in the same cell is in striking contrast with the irregularity of reaction frequently seen in neighboring cells in poliomyelitic cords. It is well known, for instance, that cells of normal appearance can often be seen in juxtaposition with severely chromatolysed cells. The fact that the earliest visible changes in the cell due to poliomyelitis are in the Nissl bodies, also suggests that the primary reaction of the virus is with cytoplasmic rather than nuclear mechanisms. However, if it is assumed that the virus reacts both with cytoplasmic and with nuclear mechanisms, it is conceivable that the virus could first multiply in the cytoplasm and at a critical level of concentration throughout the cytoplasm could then react equally with all nuclei in a multinucleated neuron. This hypothesis not only requires the assumption of a common substrate for virus in both nucleus and cytoplasm, but also contains the assumption of an astonishing precision of virus reaction with units of nuclear dimensions. It seems more reasonable to suppose, on the basis of uniformity of response of as many as six nuclei in one cell, that the primary site of reaction of virus is in the cytoplasm and that nuclear degeneration in poliomyelitis, including the formation of intranuclear inclusion bodies, is not a result of direct virus action but is an orderly process which reflects the general degradation of cell functions.

SUMMARY

Numerous multinucleated neurons were found in the brain, spinal cord, and spinal ganglia of an adolescent rhesus monkey which had been killed during the acute stage of poliomyelitis. Many anterior horn cells containing 2 to 6 nuclei showed poliomyelitic degenerative changes characteristic of those seen in ordinary neurons. A striking finding was that the nuclei in any single multinucleated cell were

invariably identical or almost identical in appearance, regardless of the degree of poliomyelitic change. The interpretation of this phenomenon led to the hypothesis that the primary reaction of virus is in the cytoplasm, and that nuclear degeneration in poliomyelitis, including the formation of intranuclear inclusion bodies, may reflect the general degradation of cell functions rather than direct virus action.

EXPLANATION OF FIGURES

All cells shown are anterior horn motoneurons of rhesus A924, photographed from 15 μ sections stained with gallocyanin. Magnification 600 $\times$.

PLATE I

Figs. 1 and 2. Cells of normal cytological appearance but with two nuclei. Note sharply stained Nissl bodies in cytoplasm, and single basophilic nucleolus in center of each nucleus. The oxychromatin is diffusely scattered throughout the nuclei.

Figs. 3, 4, and 5. Binucleated cells showing earliest poliomyelitic change, consisting of central thinning out of Nissl bodies. This is shown in increasing degree in figs. 3 to 5 respectively. The nuclei are essentially normal in appearance.

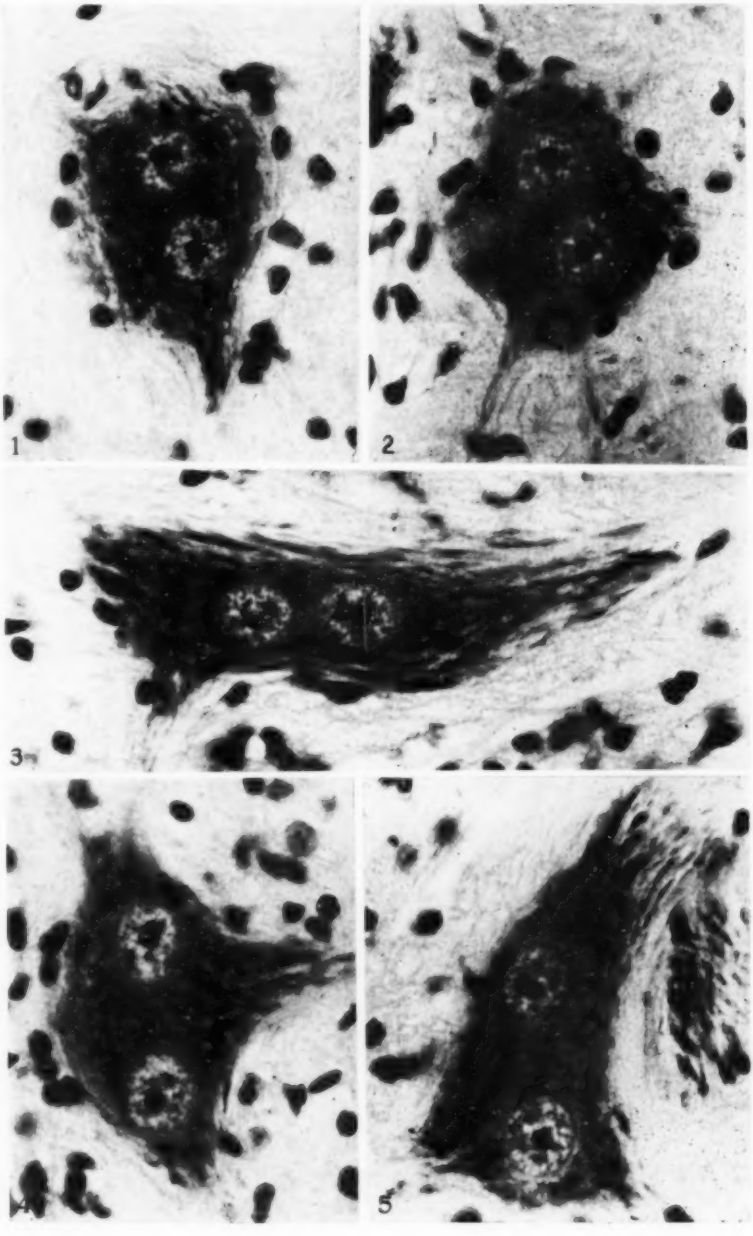

1
2
3
4
5

PLATE II

Fig. 6. Later stage of poliomyelitic change showing extensive chromatolysis in cytoplasm, eccentric position of nucleolus, and beginning aggregation of oxychromatin within nuclei (early stage of inclusion body formation). Note parallel changes in both nuclei.

Fig. 7. Cell with four nuclei, showing changes similar to those in fig. 6. The uppermost nucleus in the figure (n) is out of focus, but is at the same stage of degeneration as the other three nuclei.

Fig. 8. Cell with severe chromatolysis. Basophilic nucleoli are quite eccentric in the nuclei, and each one is next to a single large eosinophilic inclusion body (i). The inclusion body in the lower nucleus is somewhat out of focus.

Fig. 9. Stage similar to that seen in fig. 8, but with two inclusion bodies in each nucleus. One inclusion body in the nucleus to the right is at another focal level.

Fig. 10. Severely chromatolytic cell with nuclei in same stage of degeneration, and each containing a single inclusion body (i).

Fig. 11. Completely chromatolytic cell with five nuclei, of which two are in an adjacent section. The nucleus to the right in this section (n) is out of focus. All five nuclei were identical in appearance, and each contained a single large inclusion body (i).

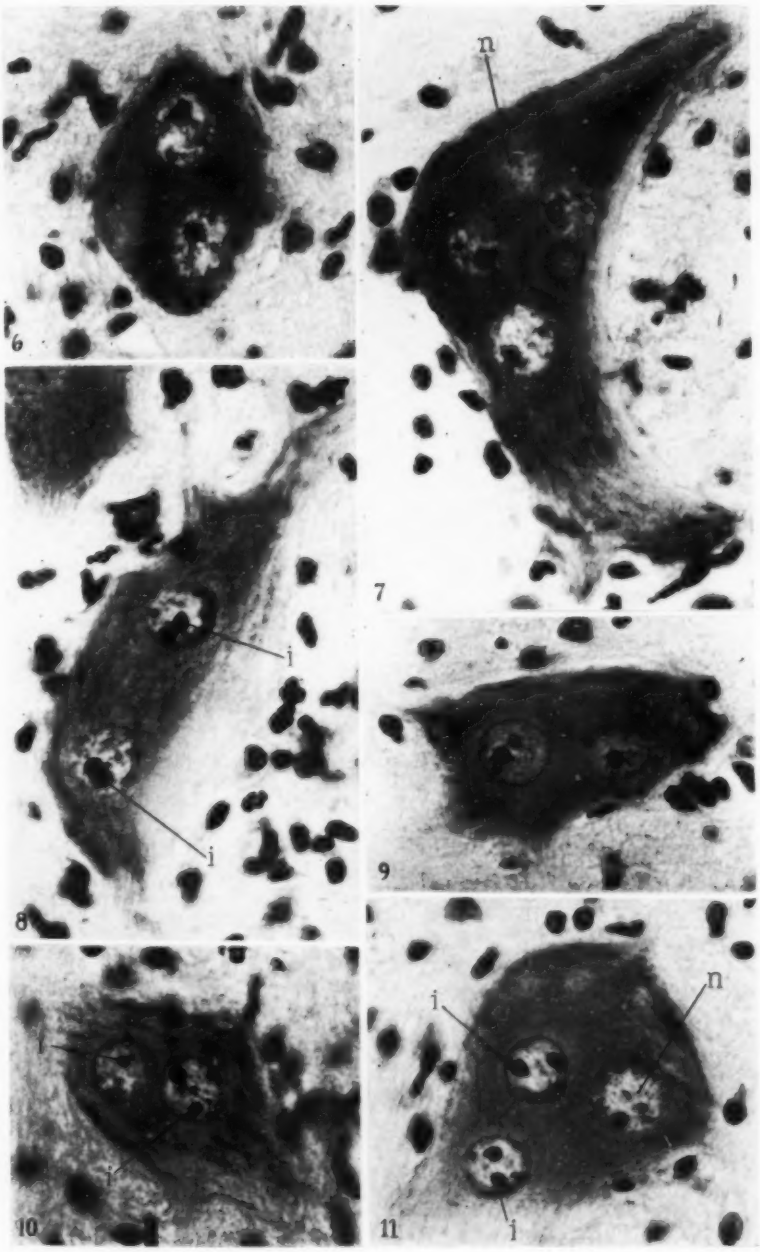
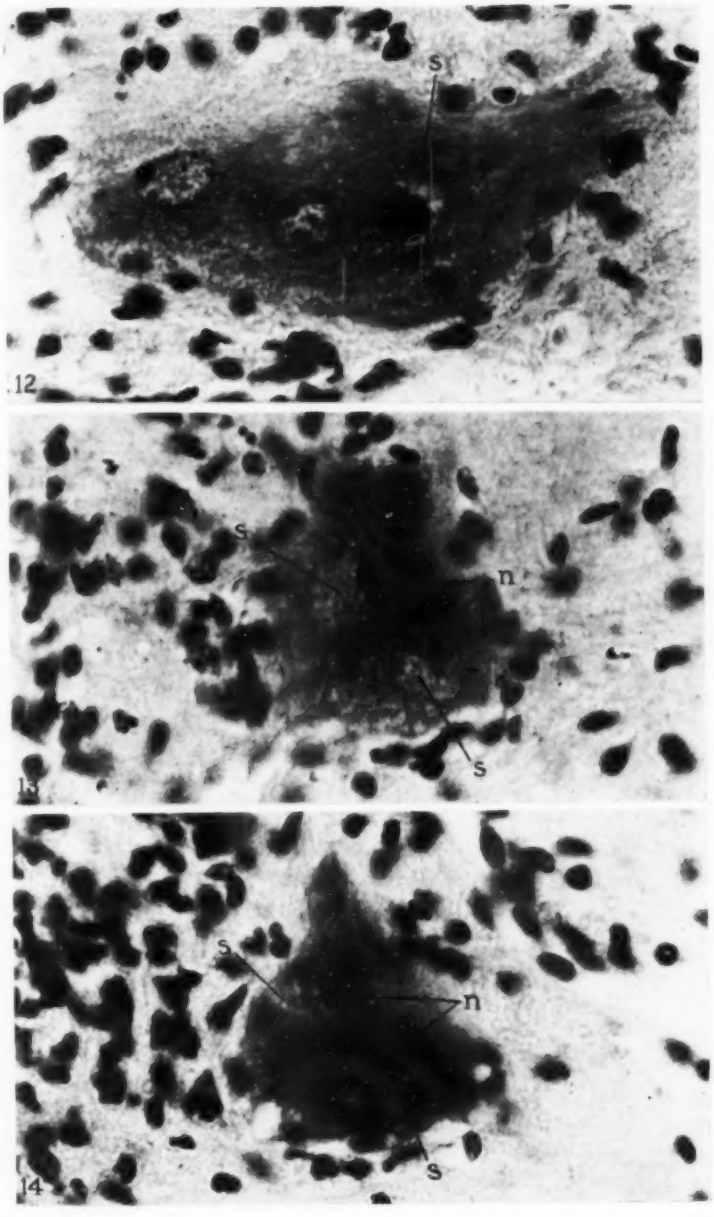

n
6
7
i
i
8
9
i
n
i
10
11

PLATE III

Fig. 12. Cell with six nuclei, of which only four appear in this section. No Nissl substance remains in the cytoplasm, which has a granular appearance, suggesting irreversible degenerative change. The nuclei all exhibit shrinkage, irregular membranes, shrunken nucleoli, small basophilic bodies, and in one case a perinuclear shrinkage space (s), probably not a postmortem change.

Figs. 13 and 14. Two sections through a necrotic cell containing four nuclei, two of which appear in each section. Cytoplasm contains no Nissl substance, but is granular and stains diffusely with gallocyanin. Nuclei (n) all similar in appearance, shrunken, irregular in outline, and containing small basophilic granules as well as the larger basophilic nucleolus. Each nucleus has shrunken within a space (s), paler than the surrounding cytoplasm, which represents the former outline of the nucleus.


s
12
s
n
s
13
s
n
s
14

THE DIETARY RÔLE OF HISTIDINE IN THE IMMATURE AND ADULT RAT[1]

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Although the rôle of histidine in the diet of the rat has been studied extensively the evidence as to its essential rôle is conflicting. The lack of clarity on the subject arises from the fact that immature rats have been observed to lose (1), maintain and gain weight (2–5) on diets in which the protein moiety was replaced by casein hydrolysates from which histidine was partly removed by mercury (4) or silver (1, 2, 3) salts or by electrolysis (5). Possibly due to the brevity of the experimental periods a lack of unanimity of opinion on the need of histidine has also resulted from studies in which amino acid mixtures were substituted for the protein moiety of the diet (6, 7).

In an attempt to clarify these matters we report herewith the results of experiments undertaken to ascertain the need of histidine in the diet of immature and adult rats by the administration of control and histidine-deficient diets in which the protein fraction is composed of a mixture of 19 crystalline amino acids for periods of four weeks. The evidence obtained from growth curves indicates that histidine is required for growth of the young rat (50–60 gm.) and the more mature rat (200–225 gm.) as well as for the maintenance of weight of the adult rat (300–400 gm.).

EXPERIMENTAL

Animals. Our observations were made on rats from a hybrid colony of albino and hooded Norwegian rats that has been in use in this laboratory for 20 years. They were kept in individual cages

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[3] Presented at the 108th meeting of the American Chemical Society, New York, September 11, 1944.

which were not designed in such a way as to prevent coprophagy. Individual litters were divided so as to obtain an equitable distribution of weight and sex for the histidine deficient (HDS) and control (CHDS) experiments. Weight measurements were made weekly.

TABLE I

*Composition of Amino Acid Mixture**

AMINO ACID	AMOUNT FED	NATURAL AMINO ACID FED
	gm.	gm.
Glycine	0.9	0.9
dl-Alanine	3.6	1.8
dl-Serine	1.8	0.9
dl-Valine	18.0	9.0
l (−) Leucine	12.0	12.0
dl-Isoleucine	16.2	8.1
dl-Norleucine	7.2	3.6
l (−) Cystine	4.2	4.2
dl-Methionine	10.8	5.4
l (−) Proline	1.8	1.8
l (−) Hydroxyproline	0.9	0.9
l (−) Aspartic acid	1.8	1.8
l (+) Glutamic acid	18.0	18.0
dl-Phenylalanine	27.0	13.5
l (−) Tyrosine	9.0	9.0
l (+) Arginine·HCl	5.4	3.0
l (+) Lysine·HCl	16.8	13.5
l (−) Tryptophane	3.6	3.6
dl-Threonine	12.6	6.3
Sodium bicarbonate	12.0	
Total	183.6	117.3

* Merck Amino-Acids used throughout.

Diets and Feeding Procedure. The composition of the histidine-deficient amino acid mixture is shown in Table I and composition of the diets in Table II. Owing to uncertainties regarding the B-complex vitamins, Brewers' yeast was used instead of a mixture of the synthetically available components of this vitamin group. On the basis of recently compiled data on the composition of yeast (8), a daily ration of 5 gm. of HDS diet would contain 1.5–2.0 mg. of histidine which apparently is not sufficient for the needs of the rat.

The control animals were restricted in their intake to 5.0 gm. of food per day for the young rats and 10 gm. per day for the adult animals. The animals on the deficient diet were fed *ad libitum* but their appetities were poor and rarely did food consumption for this group equal that given to the controls.

TABLE II

Composition of Diets

DIET	HDS	CHDS	AMIGEN
	gm.	gm.	gm.
Amino-acid mixture as fed	24.00	23.22	17.00
Brewers' yeast	3.60	3.60	3.60
Sucrose	12.80	12.80	12.80
Starch	35.50	35.50	35.50
Agar	2.00	2.00	2.00
Crisco	16.10	16.10	16.10
Cod liver oil substitute*	4.00	4.00	4.00
Salt mixture†	2.00	2.00	2.00
Water			7.00
l (+) Histidine·HCl		0.88	
Total	100.0	100.0	100.0
Natural amino acids fed	15.40	15.61	12.60‡

* Mead Johnson and Company.

† The salt mixture employed had the following composition (measured in gm.): NaCl 18.9, $CaHPO_4$, anhydrous, 25.0, $MgSO_4$, anhydrous, 6.86, $KHCO_3$ 44.4, KCl 2.88, Fe^{III} citrate, U.S.P., 2.21, $CuSO_4$, anhydrous, 0.24, $MnSO_4$, anhydrous, 0.15, KI 0.015, NaF 0.03.

‡ This figure represents the amount of amigen fed on a moisture and ash-free basis and natural amino acids as they are obtained by an enzymic digestion.

Results. Representative data derived from 15 rats on HDS diet, 12 on CHDS diet and 90 on Amigen diet are summarized in Figs. 1, 2, and 3. It appears there-from that histidine is required for growth as well as adult weight maintenance by the rat. These data confirm the report of Rose and Cox (1) and Wolf and Conley (6) and do not support the findings of Burroughs, Burroughs and Mitchell (7). Attention is called to the observation that the animals fed the Amigen diet grew almost twice as fast as those on CHDS diet, even though the latter diet contains 20 per cent more of the natural amino acids.

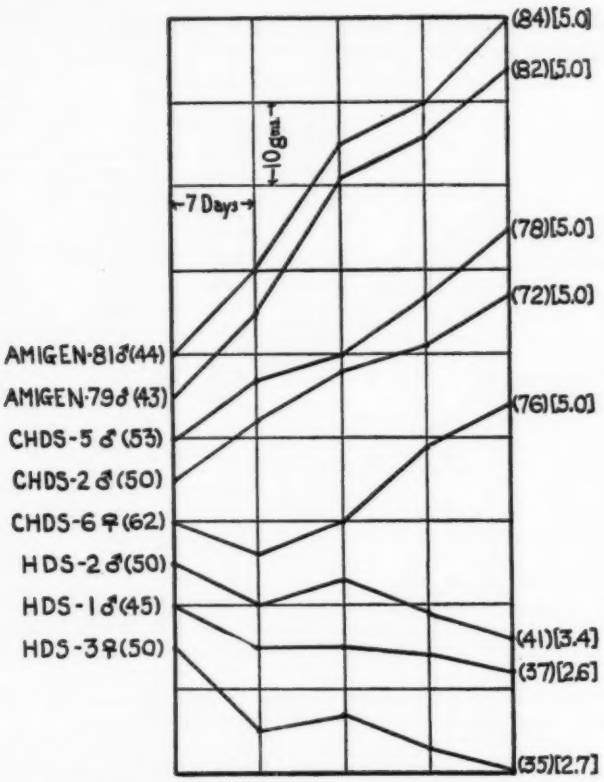

FIG. 1. THE EFFECT OF HISTIDINE ON THE GROWTH OF IMMATURE RATS

The figures in parenthesis denote body weight of animals in grams. The figures in brackets denote the average daily food consumption.

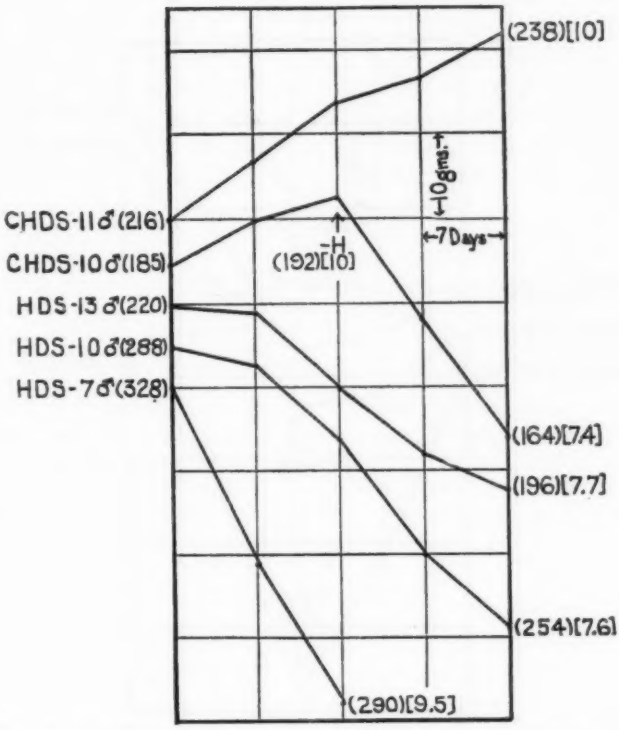

FIG. 2. THE EFFECT OF HISTIDINE ON WEIGHT MAINTENANCE OF THE ADULT RAT

The arrow (−H) indicates removal of histidine from the diet. The figures in parenthesis denote the animal weight in grams; those in brackets the average daily food intake for the diet periods.

The low growth coefficient of the CHDS diet incites speculation as to the causative factors; the following possibilities suggest themselves: (a) growth-inhibiting action due to some of the unnatural forms of the

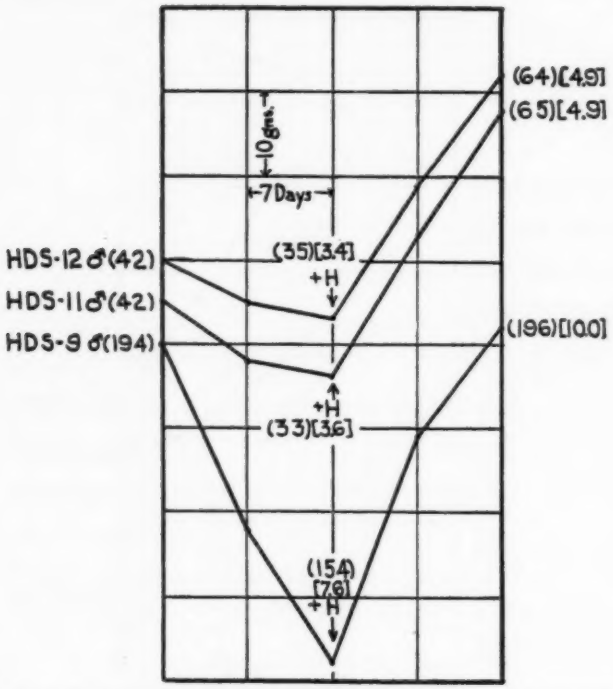

FIG. 3. THE EFFECT OF HISTIDINE SUPPLEMENTATION OF THE HISTIDINE DEFICIENT DIET (HDS) ON THE GROWTH AND WEIGHT OF RATS

The arrows (+H) indicate the introduction of histidine in the diet. The figures in parenthesis denote the body weight in grams, those in brackets the average daily food consumption.

amino acids or (b) the composition of the mixture or (c) failure to include in the diet some as yet unidentified amino-acid. Evidence for the latter conjecture can be derived from the recent report of Channon (9), who found that the lipotropic action of whole casein could not be equalled by the use of various mixtures of the known

amino-acids. The new factor could be concentrated in the butanol-soluble amino-acid fraction.

SUMMARY

By the use of amino acid mixtures it has been shown that histidine is a dietary essential for growth of young rats and for weight maintenance in the adult rat. The low growth coefficient of the synthetic diet as compared to a diet prepared with an enzymic digest of casein remains unexplained and is being investigated.

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JOHNS HOPKINS MEDICAL SOCIETY MEETING

I particularly enjoyed the presentation of Dr's. Long and White because of the opportunity a year and a half ago of working in their laboratory. At that particular time Dr. White's work on hormonal lymphopenia was just producing results. The vicarious thrill that goes through even the not-participating workers in a laboratory as occurred at that time can be especially appreciated by those of us in the surgery department here during the past few months.

As an extension of the work of Dr. Long, we have studied here the fall in adrenal cholesterol and ascorbic acid following burns and tourniquet shock. Both items decrease markedly. This decrease does not occur in hypophysectomized animals, indicating a possible humoral mechanism.

The effect of adrenaline injections also corresponded to a humoral theories. To test this mechanism further, studies on adrenomedullectomized and adrenal transplanted rats gave equivocal results, possibly due to scar tissue. To additionally complicate the picture, in parabiotic animals, only the traumatized partner showed a decrease in adrenal cholesterol, indicating as far as this goes a lack of humoral mechanism.

Traumatic effects on the adrenal of a qualitative nature have been recognized for some time. It seems to me that the work of Dr's. Long and White has put these changes on a firm chemical basis and they have given us several quantitative local and peripheral means of measuring such changes. This work should lead to still further elucidation of this important subject.

BOOK REVIEWS

Essays in the History of Medicine presented to Professor Arturo Castiglioni on the occasion of his seventieth birthday, April 10, 1944. Supplements to the Bulletin of the History of Medicine. Editor: Henry E. Sigerist. The Johns Hopkins Press, Baltimore, 1944.

Arturo Castiglioni,—born at Trieste in 1874, rose in his profession until he became head of the sanitary services of Lloyd Triestino and the Italian Steamship Lines, and Professor of the History of Medicine at the University of Padua. A man whose talents led him into so thoroughly cosmopolitan a vocation and avocation could scarcely be *persona grata* under a nationalist dictator, and therefore Castiglioni was forced to leave Italy in 1939 and to celebrate his seventieth birthday last year in a foreign land. The nostalgia of an anniversary in exile must have been to some degree solaced by the presentation of this testimonial volume, to which 26 of his friends contributed essays in the history of medicine. The book not only pays a fine tribute of friendship and admiration to Castiglioni—it typifies the spirit of international fellowship among scholars, which nationalism, however malignant, will never suppress.

The essays come from seven countries and are written in five languages. It is not possible, in a brief review, even to name all the contributions, much less to discuss them all justly. They provide a varied array of interesting papers, from which the reviewer can only mention a few that happened to attract his own special attention. Juan B. Lastres of Lima writes interestingly and conservatively about the medicine of the Peruvian aborigines and the sources for its study. Juan Ramón Beltrán of Buenos Aires contributes a short piece in a characteristically Latin-American literary form, a prose poem stating some ever-important generalizations about the history of medicine, in elevated language. Carlos Martínez Durán narrates the astonishing, and to North Americans little-known, history of colonial hospitals in Spanish America, listing 25 hospitals known to have been in existence before the Pilgrims landed on Plymouth Rock. John F. Fulton of Yale pays his tribute to Castiglioni very aptly with an account of another transplanted Italian scholar, Polydore Vergil. Leonardo Olschki tells entertainingly about medical matters in Marco Polo's book of travels. George Sarton revives the memory of the 15th centruy penologist Beccaria. Adolf Magnus-Levy writes about diets for diabetics in the pre-insulin era. From our own Johns Hopkins Institute of the History of Medicine Ludwig Edelstein concocts a brief but delightful essay about Sydenham's advice to Sir Richard Blackmore, to read Don Quixote in preparation for the practice of medicine. His colleague E. H. Ackerknecht sympathetically narrates the life of Paul Bert as physiologist, statesman, and colonial administrator. Among these and the other articles in the volume any physician who is at all interested in the history of medicine will find pleasantly instructive reading; but what is more important, he will complete his perusal of the volume with a renewed sense of the world-wide and timeless traditions of our

profession. The book contains a brief biography and bibliography of Professor Castiglioni and a portrait which does not do justice to his urbane and expressive countenance.

G. W. C.

"Gynecological and Obstetrical Urology." By Houston S. Everett. 503 pp. Price $6.00. Williams & Wilkins, Baltimore.

This is a book which has been long over due. The author states in his preface that he has felt the need of a modern work on female urology since he has been actively engaged in teaching the subject to medical students. The average textbook on Urology devotes almost all of its space to a consideration of the male, and the small amount of text which is devoted to the female shows a great lack of understanding on the part of the author of the association of gynecological and urological diseases. Everett has attempted in this volume to unravel some of this confusing symptomatology. How frequently the important diseases of carcinoma, tuberculosis and gonorrhea involve both the urinary and generative systems! Also, how commonly the urinary tract plays a role in major complications of pregnancy and the puerperium! For these reasons and others mentioned by the author some knowledge of urology is essential to every well trained obstetrician and gynecologist.

Everett has devoted a full chapter to the technique of cystoscopy by the air method, which was originated by Howard A. Kelly in the clinic of which the author is now in charge. The chapters on diseases of the urethra, inflammations of the bladder, incontinence of urine, retention of urine, ureteral obstruction and renal infections should be of special interest to all gynecologists and obstetricians. In addition to these conditions, an understanding of which is so essential to obstetrics and gynecology, the author has discussed with great clarity and understanding tuberculosis of the urinary tract, calculus disease of the kidneys and ureters and neoplastic diseases of the bladder, ureters and kidneys.

The book has been attractively composed and printed by the publishers. A few of the masterpieces of medical illustration by Max Brödel have been taken from Kelly and Burnam's excellent early work on "Diseases of the Kidneys, Ureters and Bladder". New illustrations by contemporary medical artists are of good quality and are liberally used. Great numbers of urograms are also clearly reproduced. This single volume work will serve as a suitable textbook for medical students and as an excellent reference work for all gynecologists and obstetricians who wish to keep abreast of urology in relation to their specialties.

R. W. Te L.

History of Surgery. By Richard A. Leonardo. 504 pages. Price $7.50. Froben Press, 4 St. Luke's Place. New York, New York.

The writing of a history of any specialized subject such as surgery presents the difficulty that ideally the writer must be both an historian and a surgeon. Dr. Leonardo brings talents from both these fields of endeavor, and presents a credit-

able history of surgery which should be read by all whose interest in this profession extends beyond the affairs of everyday practice.

The book begins with sections on primitive, Babylonian, Egyptian, Hebrew, Hindu, Chinese, Japanese, Greek, Alexandrian, Roman, Byzantine, and Arabian Surgery. These cover the first 100 pages. The next 139 pages consider European surgery up to the beginning of the nineteenth century and the remainder of the book deals with modern surgery. A special "Addenda" takes up the history of surgical specialties and the evolution of surgical societies. This section is especially valuable and could not have been written by a pure historian. Dr. Leonardo writes well and interestingly. The latter parts of the account of modern surgery tend at times to be a compilation of brief accounts of famous surgeons with too little integration into a correlated picture of the development of surgery as a whole. In some cases, readers might object to the selection of personages for citation, especially in the modern groups. As a whole, however, this selection is excellent, although membership in surgical societies rather than contributions seems to have played a role in the selection of one or two men.

The inclusion of 100 full page plates of surgical historical illustrations at the back of the book lends charm and interest to the text. These include, among others, photostats of Lister's classical article on carbolic acid and of Fitz's on "Perforating Inflammation of the Vermiform Appendix".

The statement on the jacket of the book that this is "the first history of surgery in the English language" is an exaggeration, as D'Arcy Power's "A Short History of Surgery," 1933, and Harvey Graham's anonymous and popular "The Story of Surgery," 1939, are well known. A truer statement is that of the author himself that this is "the history of surgery, seen as a chronological whole". In his own bibliography, which is excellent, the author lists the books of Power and Graham. This book should be read by surgeons and by those studying to become surgeons.

H. N. H.

Malaria in the Upper Mississippi Valley: 1760–1900. By Erwin H. Ackerknecht. 142 pages. Price $2.00 paperbound. Baltimore, The Johns Hopkins Press, 1945. (Supplements to the Bulletin of the History of Medicine, No. 4).

This volume conforms to the usual excellent standards of the productions of the Institute of the History of Medicine. The subject under consideration is one of great timeliness, especially in view of the expected return of large numbers of soldiers who may act as potential sources of malaria. The rise and fall of malaria in the Upper Mississippi Valley, like the rise and fall of the Roman Empire, is partly explainable by many theories. These are all discussed by the author and a proper evaluation given to each. The early frequency of malaria in the Central States influenced local history considerably to give one example, cited by the author: if it were not for malaria, the Mayo Clinic might now be in Lafayette, Indiana, rather then in Rochester, Minnesota. In 1854, tired of the debilitating chills and fever of malaria every summer, William Worall Mayo with his wife

hitched up horse and buggy and left Indiana for the healthier (then, at least) climate of Minnesota.

This book is timely, scholarly, and interesting reading to laymen, physicians, and historians.

H. N. H.

Medical Gynecology. By James C. Janney. 389 pp. Illus. $10 W. B. Saunders Co., Philadelphia and London.

The material is not divided in the way that is followed in most books on gynecology. The author approaches the subject from the point of view of the patient's complaints. It is stated in the preface that the scope of the book is limited to office gynecology and that it is written with two purposes in mind. The first is to aid the medical student in correlating the didactic lectures with the experience obtained in the gynecological clinic; the second to provide refresher material for the general practitioner. In this reviewer's opinion, the author is most successful in accomplishing both aims. The medical student as well as the practitioner will profit greatly by reading this book and having it accessible for quick reference. However, while there is a tremendous amount of information in Janney's Medical Gynecology, the material is not arranged in a way that would be apt to give the student a comprehensive grasp of the specialty of gynecology. Therefore, it is not to be recommended to the student who will have only one book on this subject.

L. B.

Military Medical Manuals. Manual of Clinical Mycology: Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. 348 pages with 148 illustrations. Philadelphia and London: W. B. Saunders Company, 1944. Price $3.50.

Without a single reservation this book is recommended to students, medical and surgical practitioners, dermatologists, and clinical mycologists as the finest book on the subject that has been written. Furthermore, the authors have done such a commendable piece of work in assembling and presenting the contents that it will be difficult for anyone or a group of scientists to produce a superior manuscript on the subject. The manner in which the book has been compiled is solely responsible for its excellence. The sections on mycology, pathology, immunology and hypersensitivity, and symptomatology and treatment have been prepared repectively by Doctors Normal F. Conant, Roger Denio Baker, Donald Stover Martin, and David Tillerson Smith and Jasper Lamar Callaway each being particularly well educated and experienced in his own field and ably conversant with the subjects of his co-authors. Any difference in the style of writing that the authors might have had has been cleverly hidden by the uniform blending of their contributions by Dr. Martin. The subject has been covered completely in a concise and clear manner. The illustrations are plentiful, beautiful and practical. There are helpful chapters on elementary mycology and laboratory

contaminants. The appendix contains a formulary and sections on mycologic, pathologic, immunologic and dermatologic methods. The index is accurate and complete.

E. L. K.

Stokes, JOHN H., M.D.: Modern Clinical Syphilology (Third Edition). W. B. Saunders Co., Phila. Pa. 1944

The third edition of this monumental monograph lives up to the high standard set by the first two editions. The first edition appeared in 1926, and was the single handed achievement of Stokes; in the second, Beerman and Ingraham with others, appeared in the capacity of associated collaborators; in the present edition these two become full fledged co-authors.

It is unfortunate that the book appears at a time when so much concerned with the serologic diagnosis of syphilis and its therapy is in such a state of uncertain flux. Penicillin promises to outmode the metal therapy of syphilis, but is so recently introduced as to permit only the briefest preliminary discussion.

As in previous editions, the book loses value for the genuine student of the disease by the omission of a bibliography, a defect which the authors recognize but colud not help because of limitations of space.

No physician seriously interested in syphilis can afford to miss possessing a copy of each new edition of Stokes as it appears.

J. E. M.

Neisser, A., On Modern Syphilotherapy with Particular Reference to Salvarsan, translated by I. VON S. WARTENBERG; bibliography by F. T. GARDNER. The Johns Hopkins Press, Baltimore, 1945.

This little booklet of 42 pages provides a brief biography of Albert Neisser, the discoverer of the gonococcus, and independently of Schaudinn (who however obtained prior publication), the co-discoverer of the T. pallidum. In the field of syphilis Neisser is best known for his monumental experimental study of the disease in apes.

The translation is of Neisser's brief monograph on the treatment of syphilis with salvarsan (arsphenamins) and is now of historical interest only. Neisser fell into the same trap as many of his less worthy successors in the use of the word "modern" in his title. The developments of the past two years indicate the impermanence of modernity.

Neisser's complete bibliography is provided.

J. E. M.

Operations of General Surgery. BY THOMAS G. ORR. 723 pages. Price $10.00. W. B. Saunders Company, Philadelphia and London, 1945.

This book comes in a handy one-volume format. It has far more advantages than it has objections. It describes lucidly one or two examples of each of the

important procedures in general surgery. In choosing the technics for exposition the author has used good judgment, although obviously not all would agree with the choices in one or two individual instances. Thus, in the discussion of bone grafting for ununited fractures two methods, mainly those of Campbell and of Albee are listed, while other simpler methods might be more applicable to the needs of the general surgeon. However, the operations listed are almost invariably the best available at the present time. Furthermore, the text is strictly up-to-date and such technics as ligation of patent ductus arteriosus and pancreatectomy receive detailed attention. All procedures which are described are done so accurately and lucidly. The technical details are excellent and the good illustrations are well correlated with the text.

This book is the best one-volume text on operative surgery which has appeared for some time. It should have an especial appeal to general surgeons and to surgical internes and residents.

H. N. H.

Ourselves Unborn. By George W. Corner. Yale University Press, 1944. 188 Pages with Index. Price $3.00.

In Ourselves Unborn Dr. Corner is seen in his true light: distinguished embryologist, lucid author and sincere philosopher. In fact it is probably his capacity in the latter discipline which gives this small volume such unusual merit.

The book represents the substance of the 1944 Terry Lectures given at Yale University. In the preface Dr. Corner states what he proposes to accomplish: "to present a brief description of human development, its biological significance, and its aberrations, taking into account many recent discoveries, and emphasizing certain particular aspects which seem important for those who would construct their philosophy of life upon human realities."

The book is divided into three sections. The first is concerned with normal anatomical and physiological embryogenesis. It begins with a discussion of the unfertilized ovum and ends with the eighth week of intrauterine life. There is a very interesting interpolation on the development of our knowledge concerning fertilization. Dr. Corner, also, very clearly distinguishes and explains the four major types of placentation: the epitheliochoaial, syndesmochoaial, endotheliochoaial and hemochoaial.

This last section of the book is elucidated by pen and ink sketches, photographs of microscopic sections, highly magnified gross material, and wax models.

In the second section the author discusses the embryology of the abnormal or defective embryo—in yesterday's words, monsters. He traces the history of our knowledge concerning them and in the compass of twenty pages summarizes modern views. He writes: "most types of abnormalities which have been traced to their first appearance are found to begin in early development. The more they are studied, the more they are seen to represent, so to speak, orderly disturbances of the normal patterns of development". He then assesses the dual forces of heredity and environment: "either a bad egg in a good environment, or a good

egg in a bad environment, can become abnormal in the same way." As evidence he presents the study of rumplessness in fowl. The action of embryonic organization centers is discussed—the action "is due to chemical substances which they produce and transmit to the neighboring responsive tissues" and "anything which interferes with the process of organization at a given point will necessarily produce much the same sort of injury." The earlier the injury the more widespread will be the disturbance of growth; late injuries tending on the other hand to cause local lesions.

The truly religious spirit of the author is well brought forth in these closing sentences of Part II. "The study of prenatal defects, while abolishing superstition, has thus extended the known range of natural mortality and deepened the riddle of fate; but does it not strengthen the call of duty and aspiration? Those of us who survive are truly the elect, chosen from a larger multitude. In this fact we may take a melancholy pride, like soldiers who close the ranks and march on when their companions fall. Let us make all we can of this life, we are fewer than we thought."

Part three is called "The Generality and Particularity of Man", and deals with the mammalian tree and man's place in the schemata suggested. Studies in comparative embryology of the various mammalian orders have and will continue to contribute much toward the reconstruction of the actual tree.

Dr. Corner deflates man's conceit in his super-qualities by writing, "The ancestors of the Hominidae were among those which (relatively speaking) held to the middle of the way. . . .This is crudely apparent when one considers that there is scarcely any purely physical activity in which man is not excelled by some other animal—neither running, swimming, diving, flying, climbing, nor in withstanding heat and cold, nor in the use of any of the five senses."

In the final pages Dr. Corner claims that man's strengths and abilities are tied up with this anatomical versatility, this lack of physical specialization.

"The way of an eagle is to fly, the way of a fish is to swim, but a man's way is to kill or to cultivate, to grovel or stand erect, to dissipate or to build. Because he has a generalized body he can eat any diet, live in jungle, prairie or upland, swim across rivers or scale mountains, build altars to many gods. . . the scope of the human mind, the freedom of human decision, are bound up inextricably with the generalization of the body."

"Ourselves Unborn" is a stimulating book for any one interested in science or philosophy. It cannot be read like a novel, but the study and thought required are well invested. No one can read it without increasing both his cultural horizon, and his admiration for George Corner.

A. F. G.

Peripheral Nerve Injuries: Principles of Diagnosis. By Webb Haymaker and Barnes Woodhall. 227 pages. Price $4.50. W. B. Saunders Company, Philadelphia, 1945.

It has been said that despite its many drawbacks, war does have a few advantages. This book represents one of these advantages. With a mass of clinical

material to draw upon that seldom, if ever, is seen by any group of neurosurgeons in peacetime, the authors have presented an authoritative text which is the leader in its field. The drawings are superb. Clinical tests for nerve impairment, often a difficult subject for student and clinician alike, are made clear in a dramatic fashion. This book makes the principles of diagnosis of peripheral nerve injuries so up-to-date that the reader will not be satisfied until this group of army authors, or other equally well qualified, publish the necessary companion volume on "Principles of Treatment." So much that is new in this latter field has happened in the past few years: tantalum foil and sutures, Tarlor's plasma clot suture, etc., that a treatment volume is needed. However, this present volume does just what its title says and does it excellently. It will prove a boon for students, industrial and traumatic surgeons, and neurosurgeons in particular, and to all neurologists and general surgeons. This book is a complete and readable presentation of its subject.

H. N. H.

Proceedings of the Rudolf Virchow Medical Society in the City of New York. By Franz M. Groedel. Bruno Kisch and Erwin Schiff. Price $2.00. 103 pages. Brooklyn Medical Press, Inc., New York, New York.

This represents the abstracts of a number of papers given before the Rudolf Virchow Medical Society of New York in 1944. This Society, founded in 1851, includes many refugee physicians and surgeons, although its membership is not restricted to such. The papers listed cover a variety of medical and surgical subjects.

H. N. H.

Surgical Disorders of the Chest: Diagnosis and Treatment. By J. K. Donaldson. 364 pages. Price $6.50 clothbound. Philadelphia, Lea and Febiger, 1944.

The last fifteen years, since 1930, have seen enormous strides in the advancement of thoracic surgery. Many of these advances are so recent that they had as yet not been incorporated in book form. The present volume represents practically the only attempt in the English language at such a synopsis and correlation of the recent advances in thoracic surgery. (Graham, Singer and Ballon's classic volume on the subject, was published in 1935.) At first glance it maybe seen surprizing that so many textbooks of abdominal surgery have been published while so few have been printed on thoracic surgery. The recent development of the latter field explains this disparity.

It could be said the Donaldson's book would be under any circumstances the best recent volume on chest surgery because it is the only very recent one on the subject. This hypothetical statement underestimates the value of the book. It is complete, although brief, and systematically discusses all aspects of the surgical treatment of thoracic disease including lung abscess, empyema, bronchiectasis, tuberculosis, lung carcinoma, open and closed chest wounds, and other well recognized subdivisions of the subject as well as more recent aspects of interest

such as direct anastomosis for carcinoma of the esophagus, blast injuries, and the relation of the thymus gland to myasthenia gravis. The bibliography includes articles published in 1944.

The book discusses diagnosis, physiology (there is an excellent section on mediastinal flutter and open wounds of the chest), indications for treatment and detailed technical advice concerning operative procedure.

Chest surgery cannot advance as rapidly as it should until general practioniers and internists are aware of just what thoracic diseases are amenable to surgical therapy. This book gives these men a bird's-eye view of the possibilities of such treatment and should be read by all such physicians. The day when most institutionalized victims of carcinoma of the lung die in tuberculosis sanatoria should soon pass. Medical students of today will practice medicine at a time when chest surgery will be even more advanced than it is today. This book offers a foundation for such further knowledge. In addition, the book offers a good survey of the field for general surgeons and a good review of the subject for specialists. This reviewer can agree with the Journal of the American Medical Association that "this is the best handbook on thoracic surgery yet published".

H. N. H.

Textbook of Abnormal Psychology. By Roy M. Dorcus and G. Wilson Shaffer. Third edition. 547 pages. Bibliography of 833 titles. The Williams & Wilkins Co. $4.00.

The two previous editions of this book have been extremely well received and the revised edition promises to be equally popular. The authors have a broad viewpoint and present a resume of recent experimental studies in a clear and comprehensible way. No radical departures have been made in this edition, but the material has been brought up to date, including over 300 new references.

O. R. L.

The Story of a Hospital: The Neurological Institute of New York, 1909–1938. By Charles A. Elsberg. 174 pages. Price $3.50 clothbound. New York, Paul B. Hoeber, Inc., 1944.

This interesting account of the founding and development of a specialty institution should be of interest to neurologists, neurosurgeons, medical historians, and hospital administrators. Written by Charles A. Elsberg, one of America's pioneer neurosurgeons and associated with the neurological Institute of New York from its beginning, the book is authoritative and casts sidelights on the development of neurology and neurosurgery as specialties in this country.

H. N. H.

The Woman Asks The Doctor. By Emil Novak, M.D. F.A.C.S. Second Edition 130 pp. Illus. $1.50.

New material has been added to this second edition, and some of that in the first has been revised so as to bring it up to date. However, these alterations

have not changed the style which characterized the first book. One still gets the impression that he is listening in on a conversation between the wise and kindly physician and his patient. In simple and yet clear and accurate sentences, Novak answers the many questions that worry so many women. He dispells many of the fears that are needless, while still emphasizing the importance of heeding the first warnings of any serious pathology. It would be well for every woman to read this book, and even the physician can learn much from it.

L. BRADY

American Surgeon Abroad. BY RICHARD A. LEONARDO. 235 pages. Price $2.50. Froben Press, New York City, 1942.

This book should be read by everyone contemplating postgraduate study in surgery in Europe after the war. Despite the destruction caused by the conflict, many medical centers, e.g. Edinburgh, remain practically unscathed. If the period after the last war serves as any indication of what may happen this time, many surgeons will seek postgraduate experience abroad.

In general, there are two groups of surgeons who travel abroad: the first group comprises those who have already completed a residency in this country and wish to meet European leaders in surgery and compare their methods with those at home. The second group consists in those who have not completed a residency in this country and who must obtain the bulk of their experience abroad. This book is primarily written for the second group. Thus, the work in various clinics which present formal instruction to foreigners: Edinburgh, London, Berlin, Vienna, Budapest, Pecs, and Debrecen, is described in details. Particular stress is placed on the actual operative experience which can be obtained in Hungary. This aspect of the book is excellent. It might be said, however, that if the book could have mentioned more of the leading present day European surgeons, it would have had more appeal to the first group. Thus no mention of leading living British surgeons is made except of Illingworth of Glasgow. In Germany, Sweden and Russia no surgeon is mentioned by name and in France, Hartmann and Pierre Duval get citation. To all surgeons intending to visit Europe, it would have been interesting to include a mention of Trotter, Gordon—Taylor, W. C. Wilson, Joll, and Morley; of Von Haberer, Kirschner, Sauerbruch, Konjetzny, Schmieden, Payr, Magnus, and Bauer; of Nyström, Hellström, Hultén, Crafoord and Einar Key; of Judine; and of Cunéo, Lenormant, Leriche, Gosset, and Lambret, respectively in the countries cited. As the author states in his preface, he does not describe clinics which he did not visit and this honesty is to be commended. It is a pity that his peregrinations did not include more well known clinics as his descriptions of those he did visit are accurate, informative and interesting. This book is the leader in its field and should be consulted, let it be repeated, by all contemplating a visit to European surgical clinics after the war.

H. N. H.

Casualty Work for Advanced First-Aid Students. By A. W. Macquarrie. Edinburgh, E. & S. Livingstone, Ltd. 231 pages. Price $1.80 clothbound. Peter Reilly Co., Philadelphia, U. S. Agents, 1944.

This book is little larger then the palm of one's hand, but is filled with useful information concerning the case of the injured especially in wartime and contains a useful index. The advice is strictly up-to -date as is evidenced by the section on burns which advises clean plain or vaseline gauze as a first aid measure. The book will be of more use to civilian first-aid students than it will be to physicians.

H. N. H.

Approved Laboratory Technic: Clinical Pathological, Bacteriological, Virological, Parasitological, Serological, Biochemical and Histological. By John A. Kolmer and Fred Boerner. 4th Edition 1017 pages, Price $10.00. D. Appleton Century Company, Inc., New York, 1945.

This book, first published in 1931, had had new editions in 1938, 1941 and in 1945. The present edition is in no way inferior to its predecessors and the volume still ranks as one of the best manuals of laboratory technic in the English language. Because of the eminence of the authors in the field of bacteriology, those sections of the book relating to that science are naturally up to date. Furthermore, in looking over the chapters in a field less germane to the chief work of the writers, namely the section on "Chemical Methods", the reviewer was pleased to note the inclusion of many recent developments. Examples of these are the Frame, Russel and Wilhelmi method for the determination of amino acid, the Ormsby method for the determination of urea nitrogen, and particularly the Phillips copper, sulfate method (for the determination of specific gravities of whole blood and plasma). The inclusion of such collaborators as the following helps to explain the well-roundednature of the book: J. Harold Austin, Henry L. Bockus, Abraha m Cantarow, Harr y Corper, Israel Davidsohn, Thomas Fitz-Hugh, Jr., Earl W. Flosdorf, Russel H. Haden, Frank W. Konzelmann, Kenneth M. Lynch, and Thomas B. Magath.

The book serves as a ready and modern guide of the important laboratory tests for clinicians who are interested in the intervelation of such tests and for laboratory workers who do the tests.

H. N. H.

Clinical Lectures on the Gallbladder and Bile Ducts. By Samuel Weiss. 504 pages, Price $5.50. The Year Book Publishers, Inc., Chicago, 1944.

In a series of thirty lectures (one on radiology of the gallbladder by Ernest E. Smith, one on diagnostic and therapeutic duodenal drainage by Harry M. Eberhard, and the rest by the author) the various aspects of gallbladder and biliary tract disease and discussed. Chief emphasis is placed on diagnosis and medical management, but the indications for surgical treatment and a discussion

pre- and postoperative care are listed. The bibliography is adequate and up-to-date and modern subjects such as liver function tests and hypoprothrombinemia are thoroughly covered. This book is a luicid exposition of the subject matter under consideration and should serve as a useful and reliable guide for medical students, gastroenterologists, internists and, from the diagnostic and pathologic standpoints, for surgeons.

H. N. H.

Duodenal and Jejunal Peptic Ulcer: Technic of Resection. By Rudolf Nissen. 143 pages. Price $4.75. New York, Grune & Stratton, 1945.

This book, with a foreword by Dr. Owen Wangensteen, represents the fusing of Continental and American ideas concerning that common and important operation: gastric resection for peptic ulcer. The migration of intellectuals westward from the Byzantine Empire is one of the explanations for the Renaissance. Similarly American Surgery cannot help but profit by the inclusion of such distinguished European surgeons as Nissen, formerly first assistant in Sauerbruch's Clinic in Berlin, for six years Professor of Surgery at Istanbul, and a noted contributor to chest and abdominal surgery in his own right before coming to this country. Nissen's Continental origin gives added weight to his opinion on this particular subject. It is generally recognized that American surgery has for some years been generally superior to Teutonic surgery, but in the 1920's and early 1930's gastric surgery, at least insofar as a proper appreciation for gastric resection in ulcer is concerned, was somewhat more advanced in Germany than in this country. The pendulum has now swung the other way, but during the period when continental surgeons were stealing a march on us, so to speak, Nissen was one of the leaders in that advance. Putting it another way, the superiority of German surgeons in gastric surgery during the 1920's and early 1930's possibly representes the last flicker of the candle of leadership for the lands of Langenbeck, von Bergmann, and Billroth in a major field of surgery for some time to come.

The first, and larger, section of the book considers duodenal ulcer. The author emphasizes that actual resection of the ulcer, or at least closure of the duodenum itself, is possible in most instances. The Finsterer exclusion operation is accompanied by a high mortality, is especially apt to be followed by jejunal ulcer, and is a distinctly second choice. Even when the ulcer involves the ampulla of Vater, a T-tube in the common duct will present dammage to the duct (method of Lahey). The original technic of the author for resection of the pylorus even in the presence of a penetrating ulcer into the hand of the pancreas is presented in full with the subsequent historical development of the method. It is of interest that Gohrbandt's method receives considerable attention and according the Louis Lochner, Gohrbandt was chosen to treat Hitler for the injuries received by the latter as a result of the bomb episode of July 20, 1944.

Essentially Nissen's method is the precursor of the technic described in this

country by Roscoe Graham. One cannot help reading Nissen's essay without realizing that he speaks from a large experience in gastric surgery. The book is to be commended in that it does not deal in generalities but considers definite points of technic.

The section on jejunal ulcer is equally good. The pictures are clear and their correlation with the text is excellent. This book is heartily recommended to all those interested in gastric surgery for peptic ulcer.

H. N. H.